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Quantitative Genetic Studies on Livestock Improvement and on Familial Disease in Man

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Quantitative Genetic Studies on Livestock Improvement and on Familial Disease in Man

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The material presented in this submission comprises original research publications by the author in the fields of quantitative genetics in animals and in man. The research on animal genetics was carried out between 1959 and 1968 at the A.R.C. Animal Breeding Research Organisation, Edinburgh, and the work on human genetics from 1968 to 1974 in the Department of Human Genetics at the University of Edinburgh.

Within each field of study rather more than half of the papers are theoretical or operational in nature, dealing with results of general interest or with new methodology. The rest of the papers are more practical, estimating genetic parameters and responses in animals, or dealing with specific diseases and their prevention in human populations. The object of this precis is to present and integrate the various papers, to describe the main findings of the research and to discuss their relevance in the respective fields.

Research Papers Submitted

(in chronological order)

1. Smith, C. 1959. A comparison of testing schemes for pigs. Anim. Prod. 1 : 113.

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3. Smith, C., King, J.W.B. and Gilbert, N. 1962. Genetic parameters of British Large White bacon pigs. Anim. Prod. 4 : 128.

4. Smith, C. 1962. Estimation of genetic change in farm livestock using field records. Anim. Prod. 4 : 239.

5. Smith, C. 1963. Genetic change of backfat thickness in the Danish Landrace breed of pigs from 1952 to 1960. Anim. Prod. 5 : 259.

6. Smith, C. 1964. The use of specialised sire and dam lines in selection for meat production. Anim. Prod. 6 : 337.

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10. Smith, C. and Ross, G.J.S. 1965. Genetic parameters of British Landrace bacon pigs. Anim. Prod. 7 : 291.

11. Smith, C. 1966. A note on the heritability of leg weakness scores in pigs. Anim. Prod. 8 : 345.

12. Smith, C. 1967. A note on the improvement of a trait by selection on its components. Anim. Prod. 9 : 127.

13. Smith, C. 1967. Improvement of metric traits through specific genetic loci. Anim. Prod. 9 : 349.

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LIVESTOCK IMPROVEMENT

Theoretical

The efficiency of animal testing schemes was studied in two related papers (1,2), by extending a method of Robertson (1957) and finding the optimum test design in selection which includes tested individuals. Improvement was shown to be proportional to the logarithm of the ratio (number tested/number required for breeding). The number in a test group and the type of family to test also depend largely on the above ratio, and must be varied to achieve optimum design and maximum response.

The integration of a testing system so as to achieve the maximum improvement in the breed or population as a whole was also examined (2). It was shown that maximum improvement will be obtained if testing facilities are restricted to a "nucleus" group of breeders so that there will be full opportunity for testing and selection in their stocks. The nucleus breeders can then supply the rest of the population with improved breeding stock, either directly or indirectly through a group of multiplier breeders.

In designing and comparing animal breeding schemes, the optimum selection procedure for each plan is usually required. A simple empirical expression relating the selection differential to the intensity of selection was developed (18). This expression allows simpler algebraic solutions to many optimisation problems, than is possible with the conventional formula for selection differentials from truncation of the normal curve. The expression was used to find the optimum intensity of selection for maximum response in mass selection, balancing the gains in response from intense selection with losses in performance through inbreeding (18).

Realisation of the need to measure genetic change in livestock came late in the development of animal breeding theory. Two methods are now commonly used in practice. One uses an unselected random-bred control group for comparison with the selected population. The other is based on a method developed by the author (4) to estimate genetic change from field records. This method uses the intra-sire regression of progeny performance on time relative to the population trend. It is now widely used, especially with dairy cattle, and may also become the preferred method with other species if semen can be frozen and stored indefinitely. Use of these methods has led to the critical appraisal by geneticists of the effectiveness of selection and improvement programs.

Another subject studied theoretically was the use of specialised sire and dam lines in improvement of meat production. The sire line is selected solely for growth and carcass traits, while in the dam line reproductive performance is also considered. It was shown (6) that the rate of improvement through specialised lines is never less than in a single line and may be much larger. However, this will be the case only if there are unfavourable genetic correlations between reproductive performance and growth and carcass traits and if there is a certain balance between the economic values and the heritabilities for the two sets of traits. These results were later confirmed and extended by Moav and Hill (1966). In practice the advantages in crossbreeding and in selection among combinations of different lines should make the development of specialised lines worthwhile (Moav, 1966).

The possibility is often raised that direct selection for a trait may not be the most effective method of improvement and some indirect method of selection may be preferable. Searle (1966) has

examined the value of indirect selection through a correlated trait. Two other cases were examined by the author. In one study (12), it was shown that selection directed at component items of a composite trait (a product or ratio of the items) might well be more effective than selection for the composite trait itself. However, this is likely only in special situations, such as when there are marked differences in the heritability and in the variation of the traits concerned and when the traits are highly correlated.

The other case of indirect selection studied, was the improvement of metric traits through known genetic loci. Much research effort was devoted to this possibility following reports of associations between blood group factors and economic traits. It was shown (13) that known loci which affect metric traits may be useful in improvement, their value depending on the proportion of the additive genetic variance they contribute relative to the heritability of the trait concerned. However, their use in practice is likely to be limited to cases with large confirmed effects and when normal selection methods are ineffective. In two large-scale studies on blood group factors and serum proteins in pigs (14,15) and in a survey of the literature (13), there appeared to be no known loci that could be used with confidence in improvement work in farm livestock. Moreover, it was shown (13) how sampling errors in the genetic parameters and in the effects estimated may cause selection effort to be misdirected. Such sampling errors are likely to be most serious when the heritability of the trait concerned is low and so when indirect selection appears to offer most scope.

Applied

Estimation of genetic parameters is an essential and routine part of research in animal breeding and in its application in practice. To derive this necessary information, heritabilities of a large number of production and carcass traits, and the genetic correlations among them, were estimated for the two main pig breeds in Britain from data on pigs tested at the National Testing Stations (3,8,10). There was good agreement in the parameter estimates from these studies and with estimates from other studies in the literature. Heritabilities for most traits were moderate to high, showing that selection would be effective. Moreover, the genetic correlations among traits indicated that there were no serious genetic incompatabilities among traits in improvement. Principal component analyses on the genetic matrices did not add materially to the understanding of the genetic relationships among the traits (3,10).

Two common defects in tested pigs required special genetic analyses. Pale muscle colour (9) was found to be moderately heritable. On the other hand, liability to leg weakness appeared to have a low heritability (11) and might well be ignored, where possible, in selection.

Reproductive traits in pigs are also lowly heritable and improvement by selection is likely to be slow and not very effective. However an improvement of litter production on crossbreeding is well established in the literature. In a large scale analysis (7) of British pigs, substantial advantages (5 to 12 per cent) in performance were shown by crossbred litters and crossbred sows over purebreds. These results have provided the basis for recommendations on the use of crossbred (or "hybrid") pigs for commercial use.

The rates of selection and improvement were investigated in three national testing schemes (5,8,16). In Britain, progeny testing appeared to be ineffective because little selection on test results was carried out (8). In Denmark and Iowa, there were large trends in several traits, for example, in backfat thickness where the responses were twice as great as from single trait selection experiments. Using rather ad hoc methods it was found that selection on backfat thickness was limited and that only a portion of the total change was likely to be genetic in origin. However, the trends in backfat thickness continue, along with trends in several other economic traits, so the extent of the genetic change in the population trends of these countries remains unresolved.

A practical use of this research was in the development of the British pig improvement scheme. The concept of testing in a "nucleus" group of selected herds (2) was adopted and testing and selection is concentrated in nucleus herds. The performance test was shown (1) to be more effective than the progeny test and is now used (with sib-carcass information). Genetic parameters estimated in the different analyses (3,8,10) formed the basis for deriving a selection index which combines information on 11 items and by which animals are ranked and selected for 6 economic traits. To measure the rate of response (4) and to monitor the effectiveness of the "nucleus" improvement scheme (2), two random bred control herds have been established. Pigs from different levels of the breeding hierarchy are also compared annually.

Many of the same principles of testing and selection have been adopted by independent breeding companies which compete in improvement with the national scheme. These enterprises have also

made use of results on crossbreeding (7) and on specialised sire and dam lines (6,17) by selecting specialised lines and by marketing "hybrid" female breeding stock.

HUMAN GENETICS

Theoretical

A major part of the research dealt with extensions to the Falconer (1965) model of heritability of liability to genetic disease. A numerical integration method was used to derive unbiassed estimates of the correlation in liability between relatives, modifying Falconer's earlier methods and removing anomalies (19). An important finding was that low proband concordance rates in monozygous (MZ) twins are expected for diseases with high heritability, if the population frequency of the disease is low. This anomaly, of apparently quite heritable conditions having low MZ concordance rates, had long perplexed human geneticists, and the results derived (19,27) gave a satisfactory explanation. Much confusion exists in human genetics about methods of analysis for twin data and an attempt was made to present a standard simple methodology (32).

The numerical integration method to cumulate risks with a continuous underlying liability to disease was extended to allow estimation of recurrence risks with multifactorial inheritance (23). The method is able to deal with complex family histories of a disease and to take account of various other factors such as differences in liability and heritability for different severities, onset ages and sexes. A general computer program RISKMF was developed for use in genetic counselling (29) and is being used at several counselling

centres. In addition a series of risk tables for clinicians was derived for some 15 congenital abnormalities and for a large number of possible family histories (35).

Information on a continuous trait associated with a disease, such as blood glucose levels in diabetes or blood pressure in hypertensive heart disease, can be used to increase the accuracy of genetic counselling. A method was developed to combine such information with family history in deriving the recurrence risks (37). The procedure involved serial adjustments of means, variances and covariances among items following inclusion of information from the various sources. The results were later confirmed algebraically by Curnow (1974) for a few of the simpler cases. A computer program (RISKCT) was provided for routine use in genetic counselling (37).

An important use of the numerical integration methods is to generate the expected disease frequencies in relatives for a multifactorial disease. These can then be compared with observed frequencies for different relatives, and tests of the Goodness of Fit of the multifactorial model to the data can be made, and compared with the fit by other genetic models. In a more general approach, the fit by one model to data generated with another model can be used to test whether it will be possible in practice to discriminate between different models. It was shown (25) that it was indeed very difficult to discriminate between models, both in data on familial frequencies and in segregation data within families. The choice of model in estimating recurrence risks was also studied and shown to be critical only in extreme situations (44).

Genetic heterogeneity is proving to be common in simply inherited disease, and an attempt was made to derive methods for

detection of heterogeneity in multifactorial diseases (43). If a disease can be subdivided on any criterion (clinical, biochemical, statistical or physiological) then the genetic relevance of the subdivision can be tested, or the genetic correlation between the subgroups can be measured. Possible biases in the Falconer (1967) estimates of genetic correlation were assessed and it was concluded that such biases will not be important in obscuring the true genetic relationship between two disease forms (42) so that resolution of genetic heterogeneity should be possible. A summary and discussion of much of the above theoretical work with the multifactorial model was presented in an invited paper to the Royal Statistical Society (40).

Another group of papers dealt with effectiveness of methods for the prevention of genetic disease and with the effects of changes in social and medical practices on the frequency of abnormal genes in the population. In an initial theoretical study (21), the scope for ascertainment and prevention and the effectiveness of preventive methods were examined. This showed that prevention could be effective for autosomal dominant and X-linked disorders, but less so for autosomal recessive disorders and still less for familial diseases with complex inheritance. The value of a genetic register system, to record, collate and use information in the prevention of genetic disease was demonstrated (21). The changes in the frequency of abnormal genes in the population as a result of new treatments, new social and medical practices, and new techniques (such as antenatal diagnosis) were studied in two papers (30,38). These showed that there is little cause for alarm in the adoption of preventive practices. Indeed some of the preventive measures could be eugenic rather than dysgenic; that is beneficial to the gene pool rather than deleterious.

Applied

The frequency, heritability and risks of diabetes were studied in a large body of familial data collected from diabetic probands in the Edinburgh area. The discrepancy between the frequency of recently diagnosed diabetics and diabetics diagnosed in previous decades was striking and led to the definition and estimation of the 'potential frequency', that is the estimated frequency in the population at current rates of diagnosis without differential mortality (22). The potential frequency was some 4 times greater than the observed population frequency. An attempt was made to resolve the problem of whether early and late onset diabetes are distinct genetic forms, or are manifestations of the same genetic liability (26). Neither extreme hypothesis fitted the data, and it was concluded that a large degree of overlap probably exists. The problems of estimating empiric risks in a disease with variable onset age and sex incidence were studied using the diabetes family data (28). Empiric risk estimates, similar to the population 'potential frequency' described above, were derived and presented as the best available estimates.

To check on the theoretical findings on the scope and effectiveness of preventive methods, data on ascertained families with genetic disease were analysed (24). These showed that only a small proportion of individuals at risk had received genetic counselling and that many of the cases of genetic disease could have been prevented if the available information had been collated and used. A genetic register system (RAPID - a register for the ascertainment and prevention of inherited disease) was then begun (39) to test the feasibility and effectiveness of such a system in practice (21,24,33). This involved ascertaining families at risk through various sources, methods of

obtaining consent from clinicians and family members, procedures for counselling, treatment and follow-up, and details of recording and computerisation of the register system (33). The system sought an active prospective role to bring genetic counselling into the community as a form of preventive medicine, rather than in a passive retrospective role of dealing with families only after an affected child has been born. In these aspects it is the first of its kind in the world.

Analysis of Citations

An attempt has been made, in summary, to guage the impact of the submitted papers on the world literature for animal breeding and for quantitative human genetics through the listings of citations in Citation Abstracts. The citations are listed under senior author and include all references in all sources abstracted by Biological Abstracts. The number of citations from 1965 to 1974 of the papers presented in this submission are tabulated in Table 1. Some of the papers in animal breeding are still being cited some 10-12 years after publication. Some of these seem to follow a cyclical pattern, as new aspects of the field are developed. The number of citations is larger for the human genetics papers, reflecting their more recent publication and the larger literature, especially in clinical genetics. The increase in the number of citations over the years is expected, as the list of publications increases. Of the papers published before 1975, 8 out of 34 had a colleague as senior author and so are not included in Table 1. Including these may raise the total number of citations by some 20-25%.

To put the figures in Table 1 in perspective, they must be compared with those from other research workers in these scientific fields. To do this, the number of citations during 1973 and 1974 to papers (excluding books) of authoritative scientists in animal breeding and in quantitative human genetics over the same period (1960-1974) are given in Table 2. The number of citations for the human geneticists (average 90) was about three times more than for the animal breeders (average 32), representing the larger literature on human quantitative genetics. There is a large variation in citation rates, with individuals who publish often or who have key basic papers in their field receiving the most citations. During 1973 and 1974 there were some 70 citations (Table 1) to the papers presented in this submission, and this lies between the averages for authoritative scientists listed in the two fields.

There are many hazards in trying to interpret these figures as a measure of scientific impact of the papers. Papers may be cited often initially if they are topical (e.g. reference 31), or if they are refuted (see Renwick, Table 2). Review papers tend to be cited frequently, even if they contain no original work. The number of citations will also depend on the number of research workers in the field, the journal of publication and on the authors' scientific standing, as well as on the scientific merit of the findings. Most papers will be cited infrequently and will soon be effectively lost from the literature, as they are superceded by others and as the field develops. The basic important papers in the field are these which are still referred to after many years.

With these reservations in mind, the number of citations to the papers submitted here indicates that they have had a useful

impact in their fields, and their results continue to be used. It is reassuring to note that none of the papers have been descredited or refuted while many have been extended and elaborated by other workers.

Discussion

The basic theory of quantitative genetics as it applies to animal improvement is now a well developed science. Moreover, from numerous experiments with laboratory animals, substantial genetic gains in productivity can be confidently predicted from selection in farm livestock for periods of at least 10-20 generations, and for longer periods if care is taken to preserve genetic variation. Many of the problems tackled in the papers of this submission were concerned with the application of the theory in practice both at the applied and at the theoretical (operational) level. The former tend to be useful in the short term but need revision as conditions, breeding methods and breeding stocks change. The latter tend to maintain their usefulness over a long period of time and some of the papers have become basic papers in the field.

Human genetics is at present in a rapid growth phase, both in fundamental biological discoveries and in application to preventive medicine. There is considerable scope for quantitative genetics in these fields, for example in the genetic resolution of familial diseases and in the development of systems for their prevention and control. There is, however, a strong clinical bias towards abnormality, as in the research submitted here, rather than to normality. Normal genetic variation in man is a field which is comparatively uncharted. Yet an understanding of the amount and nature of normal genetic variation

in man is important, for it affects the philosophy of our institutions and of our civilisation and the future of mankind.

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I would also like to express special thanks to my parents for their kindness, inspiration and guidance in my early career and to my wife and family for their affection and support throughout the period of the research.

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Table 1. Citations from 1965 to 1975 of submitted papers with Smith, C. as senior author

Year Published	Paper No.	Year Cited											Total
		(75)*	74	73	72	71	70	69	68	67	66	65	
1959	1					2				1		1	4
1960	2					1							1
1962	3	(1)			2	5	2	2	2	2	3	4	23
	4	(1)	3			4		1	2	3	1	1	16
1963	5								1		1	1	3
1964	6	(5)	1	1		2	1				3		13
	7	(1)	1			3	3	3				1	12
1965	8	(1)				1		1		1		1	5
	10	(1)	1		1	6	1	1	4	1	3		19
1966	11	(1)		1		2			1	1			6
1967	12		1					1	1				3
	13			1			1	1	1				4
1968	14		1	2	1	2	1	2	1				10
1969	18	(2)	1	1	2	1							7
1970	19	(3)	6	7	7	3							26
	21		1	1		1	1						4
1971	23	(2)	5	3	2								12
	24		2	2	1								5
	25	(4)	5	4	4								17
1972	26	(1)	1	1	1								4
	27		1	1									2
	29	(4)	2	1									7
1973	31	(1)	5	6									12
1974	32	(1)											1
	34	(4)											4
	37	(1)	1										2
Total		(34)*	38	32	21	33	10	12	13	9	11	9	222

* Half Year

Table 2. Number of citations in 1973 and 1974 to scientific papers published from 1960 to 1974 by authoritative animal and human quantitative geneticists

Animal Geneticists		Human Geneticists	
Name	Number	Name	Number
J.C. Bowman	19	L.L. Cavalli-Sforza	124
R.E. Comstock	10	C.S. Chung	40
G.E. Dickerson	29	J.F. Crow	115
H.P. Donald	31	A.F. Edwards	73
D.S. Falconer	132	J.H. Edwards	131
R.S. Gowe	14	R.C. Elston	47
W.G. Hill	(70)	G.R. Fraser	128
J.W. James	(13)	A. Jacquard	(26)
I. Johannson	10	C.C. Li	33
J.W.B. King	11	G. Malecot	35
B.D. Latter	39	N.E. Morton	162
A. Nordskog	13		
A.L. Rae	13	W.E. Nance	74
A. Robertson	56	J.V. Neel	163
H. Skjervold	9	H.B. Newcombe	38
St. C.S. Taylor	10	L.S. Penrose	248
H.N. Turner	37	J.H. Renwick	96*
L.D. Van Vleck	55	W.S. Schull	77
		C.A.B. Smith	38

( ). Publishing for only part of the period (1960-74)

* Excludes 110 references refuting a false clinical association.

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A COMPARISON OF TESTING SCHEMES FOR PIGS

CHARLES SMITH

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ONE aspect of current schemes directed at animal improvement is the use of measurement rather than abstract judgement to estimate an animal's merit. To put animals and their measurements on a comparable basis, the central testing station which attempts to standardise the environment during testing is often used. The problem arises as to which testing scheme and which of the many possible permutations of its design are the most efficient in terms of the improvement obtained. These questions were studied in theoretical terms (Smith, 1958) based on a procedure developed by Robertson (1957) and the findings, as they relate to practice, are presented here.

TESTING SCHEMES AND THEIR DESIGNS

There are many factors which affect the extent of improvement from testing and it is important in designing a test to know something of their relative effects. Some of these factors are:

Heritability of the trait	(h^2)
Total number of animals tested	(N)
Number required for future breeding stock	(T)
Number in the test group	(n)
Size of the family from which the test group is drawn	(m)
Number of families selected	(S)
Genetic relationship between members of the family	(r)
Phenotypic correlation between members of the family	(t)

Using these symbols we can represent almost any testing situation.

The object of testing is to furnish a basis for selection among individuals and among families. Three methods of selection are considered here. In the first the whole family of m animals is chosen on the record of a sample of n of them which perform at the testing station, so $T = mS$. The family size (m) may be chosen at will within the reproductive limits of the species. In the second method, only individuals tested at the station are used for breeding stock and $T = nS$. Either the whole test group may be selected on the average performance of the group so that $m = n$, or each individual may be considered on its own performance as if effectively it came from a family of size one. In the third method the sample of n animals from each family is discarded after testing leaving $(m-n)$ animals per family for breeding, and $T = (m-n)S$. This is a method of sib selection and is appropriate when the traits in question can only be measured indirectly, such as carcass traits. Other methods of selection are possible, such as selecting on an index of individual and family performances, but these are difficult to handle by the methods used here and have been omitted.

The genetic improvement through selection depends largely on two factors; the heritability of the trait and the selection differential, the latter being the difference between the average of those selected and the average of the whole population. Robertson (1957) points out that finding the test

design to obtain maximum improvement is a question of balancing the choice in selection against the accuracy in test proof. He goes on to present a method for finding the balance point and the improvement expected thereat in the progeny test and sib test. Where the individuals tested may themselves be used as breeding animals, as in pig testing, some modifications to Robertson's (1957) procedure are necessary to find this balance point (Smith, 1958), but these do not alter the general form of his findings.

The general picture of the genetic gains expected with optimum test structure was presented by Robertson (1957) who showed them to be a function of the testing ratio (N/S) and the intra test group correlation (t). To examine in practical terms the effects of each of the listed factors and of the methods of selection on improvement, the optimum test group size and the genetic gains in each of a series of testing situations were computed (Smith, 1958). The main results from these calculations are illustrated here in a few specific examples of how the improvement was affected. Families of 4 to 10 were used for dam families (full-sibs) and of 16 to 40 for sire families (half-sibs). The correlation between members of a family (t) was taken between 0·2 and 0·4 for full-sib families and between 0·05 and 0·2 for half-sib families. These values were chosen as likely family sizes to be encountered in practice with pigs, and as correlations likely to cover many of their economic traits.

The following graphs show the form of the effects of the various variables. Their abscissae represent the number of animals tested (N) relative to the number required for breeding (T) on a logarithmic scale, and their ordinates show the genetic gains expected when the optimum size of test group is used in each instance. The gains are in units of the heritability (h^2) times the phenotypic standard deviation (σ_p) of the trait being tested. When comparing different designs and different schemes in improving a certain trait, the heritability will be a common factor. Since the genetic gains are given in units of heritability they will apply to all levels of heritability except where it affects the correlation between members of a family (t); $t = rh^2 + c^2$, where c^2 is the environmental proportion of the total variation which is common to all members of a family. In the graphs, changes in t are taken to represent changes in relationship (r) within a family and in c^2 at a constant heritability.

The first graph is to illustrate the effect on improvement of the ratio of the number tested (N) to the number required (T) and to follow the effects of variations in family size (m) and the intra group correlation (t). The improvement from testing dam families of 4 is compared with that from testing dam families of 10. In this case the whole family (m) is either selected or rejected.

The genetic gain with optimum test group size decreases as the logarithm of the ratio of number tested (N) to the number required (T), almost linearly over the range of the N/T, clearly showing this ratio to be a vital factor in determining the improvement possible. When many breeding animals are required in proportion to the numbers tested, that is N/T is low, the gains from testing become very small and the testing facilities are quite insufficient to meet the demand for selected breeding stock. In Figure 1 the improvement from testing dam families of 10 is somewhat larger than from testing dam families of 4. Throughout the study, the larger the dam family or sire family the greater was the improvement, thus showing the advantage of having as many relatives as possible in each potentially selected family.

In practice, there will be a limit to family size. Two other factors are relevant here. If family size is so large that only a few families (3-5) are tested, the genetic variation between families will be reduced. If the number per family (m) exceeds the number required for breeding (T), the proportion of families selected is greater than necessary and lower values of m will be more suitable. The genetic gains, at a constant heritability, decrease as the intra group correlation (t) rises, indicating that the more the members of a family resemble each other for other than genetic reasons, the lower the gain from testing. Close likeness of family members is commonly presumed to be due to their genetical relationship when indeed it may be largely due to similarities of their environments. These findings on the effects of the size of the variables N/T, m and t on the genetic gains from testing are borne out in the graphs which follow and apply in general in testing work.

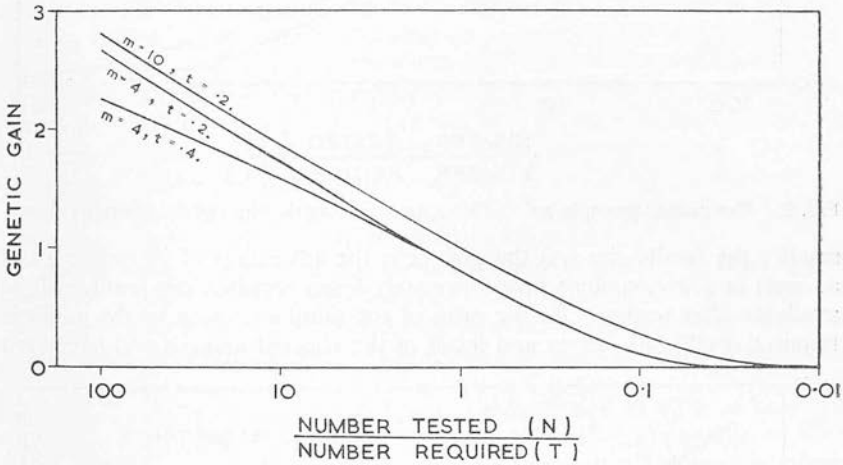

FIG. 1. The genetic gains, in units of $h^2\sigma_P$, from testing the dam families shown.

Consider selection of sire family groups (half-sibs) and selection of dam family groups (full-sibs). While family size (m) is larger in the former, the genetic (r) and phenotypic (t) relationships will be smaller. Increases in m and decreases in t make the genetic gain larger, but decreases in r make it smaller. An example showing the net effect of such changes on the genetic gain is given for a specific case in Figure 2, testing dam families of 4 ($t = 0{\cdot}3$) and sire families of 40 ($t = 0{\cdot}1$). In this case, testing dam families is superior at higher ratios of the number tested (N) to the number required (T) but the superiority is lost as the ratio decreases and testing sire families becomes more effective. The values relevant to m, t and r may alter the cross-over point of the graphs appreciably and will determine whether dam family or sire family testing is preferable for a given ratio of N/T.

Whether the individuals tested are themselves used for breeding affects the improvement considerably. To illustrate this point the genetic gains from testing dam families of 4 with an intra group correlation (t) of 0·2 are shown in Figure 3. Direct information on an individual is more accurate than similar information coming through a relative since the latter involves the degree of relationship. Hence, as in Figure 3, schemes which select only animals tested (I) or a proportion of tested animals (II), will be superior to those selecting only relatives of test groups (III) as in the sib test and progeny

test. Even when the accuracy of individual testing is low, the advantages from including tested animals in selection remain because then the whole test group rather than the individual becomes the basis for selection. The

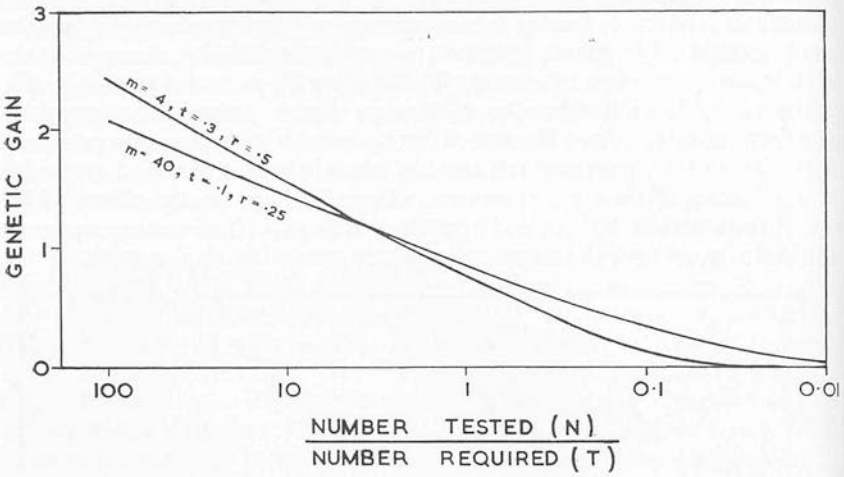

FIG. 2. The genetic gains, in units of $h^2\sigma_P$, from testing the sire and dam families shown.

smaller the family size (m) the greater is the advantage of including tested animals in selection since proportionately fewer relatives per family will be available after testing. As the ratio of the numbers tested to the numbers required (N/T) falls, fewer and fewer of the selected animals will have been

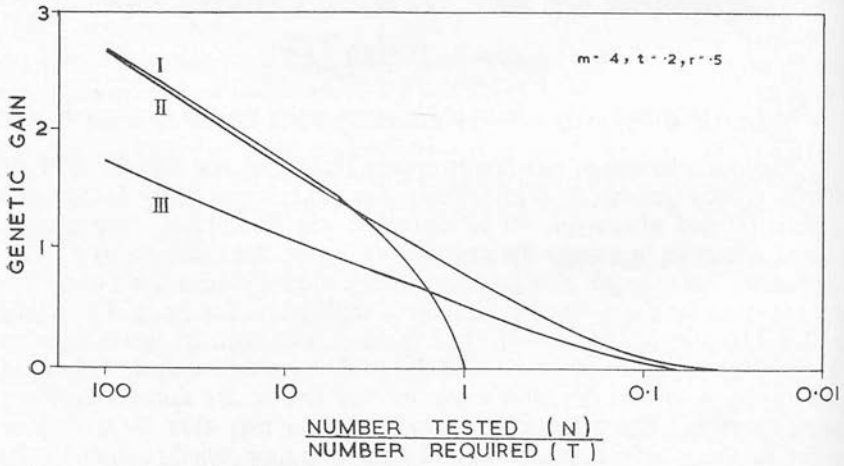

FIG. 3. The genetic gains, in units of $h^2\sigma_P$, from three methods of selection, viz.: selecting I, tested animals; II, tested animals and their relatives; III, relatives of tested animals.

tested and these will play a gradually decreasing part in the total improvement. When selection of breeding animals is made only from tested animals (I), (as if the tested animals had no relatives) the gains are appreciable till $N/T = 4$, but when $N = T$ there can be no improvement unless for example $\frac{N}{2}$ are selected on test records and $\frac{N}{2}$ are chosen at random from untested

stock. In any testing programme, selecting animals or families whose performances are poorer than average will reduce gains more than if untested stock took their place—unless it can be shown that the group of families tested are a better than average sample of the population.

The problem arises of choosing between untested relatives of one selected family and the more accurately tested individuals of a slightly inferior family. When N/T is large, almost all of each family will be tested to obtain accuracy in evaluation and n approaches m, and on the other hand, if N/T is low, accurately tested individuals of the slightly inferior families would form only a small proportion of the total selected and the effect of their inclusion or omission would be small.

In designing an efficient testing scheme, test group size (n) must be made optimum but it is apparent that optimum group size is dependent on the other factors rather than being itself any intrinsic constant in testing. Indeed it may range from one animal ($n = 1$) to all the members of the family ($n = m$). Test group size should be large when the ratio of the numbers tested (N) to the numbers required (T) is high to obtain high accuracy in evaluation, but should be small when the ratio is low to permit the testing of many families so as to yield large numbers in selection. As the intra group correlation (t) increases, members of the test group are more alike. Consequently, less new information is obtained per additional individual tested per family and the optimum group size is reduced.

Small changes in any of the factors cause only minor changes in the optimum design and the improvement. The graphs show a smooth continuous form and there is a gradual transition from one situation to another rather than an abrupt change. This makes the optimum design less critical since it appears that slight deviations are not serious. For example, the tolerable limits of group size, yielding a genetic gain of 90% or more of the maximum, showed that a fair degree of flexibility is possible without materially decreasing the genetic gains. Changes of one animal in group sizes up to 5, of 2-3 animals in group sizes from 5 to 15, and 5-10 animals in group sizes from 15 to 50 are unlikely to reduce the gains below 90% of their maximum.

POPULATION STRUCTURE AND TESTING SYSTEMS

Up to this point we have examined the aspects of improvement expected from one generation of testing. We now consider the accumulation of improvement from repeated testing over several generations and its ultimate transmission throughout the whole population. To do this, we must look beyond the narrow limits of the test and consider how the testing scheme best fits into the pig population as a whole.

The accumulation of merit in the breeding stocks can be traced through successive (y) generations if the rate of improvement stays steady. Suppose a proportion (q) of the breeding sires are supplied by the testing, then the improvement accumulated after y generations is $\frac{y}{2}\, q\Delta G$, where ΔG is the improvement per generation (Smith, 1958).

Farm livestock show a stratified structure as regards breeding operations. The commercial stock are sired by pedigreed males produced in multiplier pedigree herds which in turn buy most of their sires from a select nucleus group of breeders (Robertson and Asker, 1951 and Wiener, 1953). Gains

from placing selected animals in multiplier pedigree herds would be continuously diluted by bringing in untested sires from the nucleus group and no accumulation of improvement would result. On the other hand the breeding structure provides an efficient system for distributing merit accumulated in the nucleus group.

In devising a testing scheme to fit the breeding structure, two alternative systems of organisation may be considered. In the one, the open system each breeder may test his stock, any nucleus arrangement being ignored. In the other, the nucleus system, facilities for testing are restricted to breeders in the nucleus group. In the latter system presumably all sires needed in the nucleus group can be selected on test results, that is $q = 1{\cdot}0$. In the open

TABLE

A comparison of the improvement possible by the open and nucleus systems of testing (fuller descriptions in text)

		Open System	Nucleus System
N = 100	$\frac{N}{T}$	0·1	5
	ΔG	$0{\cdot}34\ h^2\sigma_P$	$1{\cdot}30\ h^2\sigma_P$
		Accumulation of Improvement	
Generation	1	$0{\cdot}17\ h^2\sigma_P$	0
	2	$0{\cdot}34\ h^2\sigma_P$	0
	3	$0{\cdot}51\ h^2\sigma_P$	$0{\cdot}65\ h^2\sigma_P$
	4	$0{\cdot}68\ h^2\sigma_P$	$1{\cdot}30\ h^2\sigma_P$
		Open System	Nucleus System
N = 5,000	$\frac{N}{T}$	5	250
	ΔG	$1{\cdot}36\ h^2\sigma_P$	$2{\cdot}70\ h^2\sigma_P$
		Accumulation of Improvement	
Generation	4	$2{\cdot}72\ h^2\sigma_P$	$2{\cdot}70\ \ h^2\sigma_P$
	5	$3{\cdot}40\ h^2\sigma_P$	$4{\cdot}05\ \ h^2\sigma_P$

system it has been shown that improvement will be greatest when all breeding herd sires can be selected on the basis of test results ($q = 1$) even though this is likely to reduce the average merit of selected animals (Smith 1958). Every animal or stock above the mean of the population has some potential for conferring improvement so when the demand for tested stock far exceeds the supply, the improvement is greatest when all above the mean are used.

It is possible to compare the relative efficiencies of the open and nucleus systems of testing by theoretical means (Smith, 1958). The nucleus system is likely to exceed the open system in improving the whole population after 3-4 generations and then further add to its superiority. The delay in passing on improvement to the breeding population is more than offset by the extra gains in the nucleus group. From the viewpoint of commercial stock the same conclusions apply since, assuming all sires in commercial herds come from pedigree stock, the mean of the commercial population is equal to the mean of the pedigree population in the preceding generation.

The above properties of different testing schemes are illustrated in the following example. Suppose we compare the open and nucleus systems of testing for improving some trait in a pedigree population of 1,000 herds. Say 1,000 sires are required per year for breeding. If each sire in the nucleus group can produce 30-50 sons there need be 20-30 nucleus herds to supply the multiplier breeders with sires. Suppose testing facilities are either restricted $N = 100$, or ample $N = 5{,}000$, and selection of tested animals and their relatives is practised either as full-sib families, $t = 0{\cdot}3$, or half-sib families, $t = 0{\cdot}1$, whichever is the better. The improvement possible at each generation (ΔG) and its accumulation over several generations is shown in the Table. In both cases the nucleus system soon exceeds the open system and by increasing amounts in subsequent generations.

DISCUSSION

The improvement expected in a trait following testing and selection is proportional to its heritability. Thus an efficient test design cannot make up for a low heritability. Indeed, the use of efficient designs is likely to give the same proportional increase in improvement over poor designs, irrespective of the heritability.

The measure of efficiency used in comparing different testing schemes is the extent of the improvement each provides. There are three levels at which this efficiency can be studied. The first level is concerned with the optimum design of each scheme, for example in terms of test group size. The second is concerned with the improvement expected from different testing schemes as in comparing the progeny test and the performance test; and the third deals with the impact of the testing scheme on the population of animals it is designed to improve.

Previous work on test design has dealt with the optimum test group size and composition as they affect the accuracy of a test (Osborne, 1957), and the improvement a test brings in a confined breeding unit (Robertson, 1957). The details of design of different schemes are more readily manipulated than the broader aspects of testing and can be made to fit requirements.

It is in their selection procedure that testing schemes differ basically. The progeny test implies selection among parents on the performance of their progeny, the sib test the selection between families on their sib performance, and the performance test the selection between individuals on their own performance. The designs of these schemes will differ only because the information required to select by will differ. If the tested animals can be used for breeding it is logical to include them in selection, for there will be direct information on them compared with only indirect information on their relatives. The advantage of including tested animals is considerable when they are likely to make up a large proportion of the total number selected, but falls as they constitute a decreasing proportion of the total. A common fallacy in comparing testing schemes is to assume that accuracy of evaluation is the most important factor. Dickerson and Hazel (1944) showed that annual improvement depends on a suitable combination of accuracy of evaluation, choice in selection and low generation interval. In comparing schemes all three points must be kept in mind.

The size of the test in relation to the population it is designed to improve is clearly an important factor in determining the extent of improvement. Since the improvement has been shown to be roughly proportional to the

logarithm of the ratio of the number tested (N) to the number required (T), inspection of this ratio will give a good indication of what improvement can be expected. For example in Britain there are some 14,000 pedigree pig breeding herds and 5 testing stations, each testing 1,000 pigs a year. If each breeder required one tested boar per year then $N/T = \frac{5,000}{14,000} \simeq 0{\cdot}36$ and reference to the graphs show a rather small improvement. However, it would require a vast and costly expansion of testing facilities to increase the N/T ratio sufficiently to boost improvement. In other words the testing facilities are so limited that few breeders can obtain sires of superior merit. However, with the same testing facilities (N) the N/T ratio can be considerably increased by reducing the effective size of T by restricting facilities to a number of nucleus breeders. Far greater progress can be expected if such a scheme is followed. Thus if a nucleus group of say 200 breeders were formed in Britain and each required two sires per year, the N/T ratio would be $\frac{5,000}{400} \simeq 12{\cdot}0$. The annual genetic gains in the nucleus group would then be about four times greater than if no nucleus arrangement existed. The improvement can be later passed on through the remaining pedigree herds to the commercial population. The superiority of nucleus schemes has therefore important implications in the design of national schemes of pig improvement.

Half the tested families will be poorer than average and should not be used for breeding. Robertson (1957) found that for the optimum running of any testing scheme the intensity of selection should be at least one in four. This is a goal worth aiming at in practice. However, if the number required (T) far exceeds number tested (N) it may be necessary to select animals in the second quartile for these will have some potential for improvement.

In relating these findings to practical testing schemes, it may be well to remember their theoretical origin. Certainly there are other factors affecting improvement than those studied here although it may be hard to determine their relative effects. Something that will not alter the general application of the findings but which may affect the accuracy of the results as they apply to some given situation, is the appropriateness of the heritability estimates and other parameters used. It seems that the findings will hold true in practice since the designs and schemes preferred and the improvement expected change only slowly with changes in the various factors and so seem unlikely to be radically changed by other unknown factors.

SUMMARY

Using extensions to Robertson's (1957) method for finding the optimum test design, factors affecting the improvement from testing were studied. Other than the heritability, the ratio of the number tested (N) to the number required for breeding stock (T) has the largest effect on the improvement expected, the improvement being roughly proportional to the logarithm of this ratio. The type of family and the number in the test group which compose the optimum design, also depend largely on the ratio N/T. Accuracy in evaluation is required when only few animals are selected (N/T high), but small test groups from large families are necessary when large numbers of breeding stock are required (N/T low).

Testing schemes differ basically in their selection procedure and only

secondarily in their designs. The advantage resulting from the tested animals being themselves selected is in proportion to what part they constitute of the total selected.

Another consideration is how the testing is integrated with the population breeding structure. Maximum improvement will be obtained if the testing facilities are restricted to a nucleus group of breeders, and full opportunity for selection is made in their stocks. The increased improvement this provides is accumulated in this nucleus group of herds and gradually passed down to the rest of the herds. Otherwise the improvement will be greatest when each breeder can use sires from families which have performed well in the testing.

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EFFICIENCY OF ANIMAL TESTING SCHEMES

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I. INTRODUCTION

The use of some method of testing is common in current schemes of livestock improvement. The problem arises of finding the testing procedure which is most efficient in terms of the improvement it provides. This efficiency is relevant at three levels: in determining the optimum design of a particular scheme, in comparing the improvement expected from different schemes, and in planning how a testing scheme can be best integrated with the population as a whole. Concerning the first level, Robertson [1957] and Finney [1957] derived expressions for finding the optimum test structure in animal and plant breeding respectively, so as to maximise the true superiority of chosen families or varieties tested with a given amount of testing facilities. An optimum point exists because of the antithesis under these conditions of the accuracy of selection, which increases as test group size increases, and the choice available, which decreases as test group size increases since fewer family units may be tested.

In practice the requirement of breeding animals is likely to be in terms of individuals rather than of families, say as the number of males required in the breeding herds. This variation in requirement is incorporated in an extension to the previous work in which the optimum test design and maximum gains are studied when selection comprises (i) non-tested members of selected families (ii) all members of selected families and (iii) only tested animals. In the second part of the paper we consider how best to use the testing facilities and selected individuals so as to produce the maximum improvement in the breed or population as a whole.

The expressions for genetic gain used by the above authors assume normality of distribution of breeding value. This assumption is likely to be a reasonable approximation, and moreover no more exact treatment is yet possible. Following the approach in Robertson's [1957] paper it can be shown that the genetic superiority of chosen

groups is given by

$$\Delta G = \frac{z}{p}\frac{r}{\sqrt{t}}\sqrt{\frac{p}{p+\frac{a}{K}}}\,h\sigma_G \qquad (1)$$

where p is the proportion of groups selected, z the corresponding ordinate of the normal curve, r the genetic relationship between members of the same group, t the observed intra-class correlation for the character concerned, h^2 the heritability, σ_G the genetic standard deviation, and K the ratio of the number of animals tested to the number of groups chosen. a is then $(1 - t)/t$ and the group size n is equal to Kp. The optimum value of p is then given by

$$\frac{K}{a} = \frac{2px - z}{2p(z - px)} \qquad (2)$$

where x is the abscissa of the normal curve corresponding to p. The maximum value of ΔG can then be found by substituting the optimum p value in equation (1). Over a wide range of $K/a > 5$, $\Delta G_{\max.}$ is a linear function of log (K/a).

II. REQUIREMENTS ON NUMBERS OF INDIVIDUALS

We now turn to consider the situation when the requirements are expressed as the number of individuals required for breeding. Though the requirement is stated as total individuals, the basis for selection is still the family average and the requirement may be made up of tested animals, or untested animals, or both, from the selected families. The three different cases are discussed separately.

(*i*) *Only non-tested members of selected families available.*

This will arise when tested animals are not available for breeding, as when they are slaughtered for carcass measurements. If the total family size is m, we have

$$\Delta G = \frac{z}{p}\frac{r}{\sqrt{t}}\sqrt{\frac{m}{m+a}}\sqrt{\frac{p}{p+\frac{aT}{(m+a)N}}}\,h\sigma_G \qquad (3)$$

where N is the total number of animals tested, and T the total required for breeding. This equation is of similar form to equation (1) except for the term in m and a and that K/a now becomes $N(m + a)/aT$.

(*ii*) *All members of selected families available.*

Here

$$\Delta G = \frac{z}{p} \frac{1 + (m - 1)r}{m\sqrt{t}} \sqrt{\frac{p}{p + \frac{aT}{mN}}} h\sigma_G \tag{4}$$

which is again of similar form with K/a becoming Nm/Ta.

(*iii*) *Only tested animals available.*

This is a special case since the proportion of animals selected is now independent of family size. We have here merely to maximise the accuracy of choice. Here

$$\Delta G = \frac{z}{p} \left[\frac{1 + (n - 1)r}{n} \sqrt{\frac{n}{1 + (n - 1)t}} \right] h\sigma_G \tag{5}$$

with $p = T/N$. The expression in square brackets takes the form of a U-shaped curve passing through a minimum when $n = (1 - t)(1 - r)/(r - 2t + rt)$. From the U-shaped nature of the curve it follows that the value of n which maximises improvement will be either 1 or m, since, in testing, n must be a positive integer between 1 and m. If n at the minimum is less than one, n at the maximum will be m. If n at the minimum exceeds m, n at the maximum will be 1, and if n at the minimum lies between 1 and m, n at the maximum will be either 1 or m and which can be easily determined.

III. COMPARISONS OF TESTING PROGRAMMES

With the formulae (3), (4), and (5), we can now compare the probable gains from different testing programmes. The approach used was to specify a wide series of testing situations for pigs and to find the maximum gains attainable with optimum design for different testing procedures. These results may be seen in Smith [1958]. Here several graphs are presented to show the main features of the findings. In the figure the abscissa measures the number of animals tested N relative to the number required for breeding T on a logarithmic scale covering breeding requirements of 1 to 10,000 per 100 animals tested. The maximum genetic gains are in units of $h\sigma_G$ and so apply to all levels of h^2 except where h^2 affects the correlation t between members of a test group. The graphs are these calculated for dam families of 4 and 10 ($t = .2$ and $.3$) and for sire families of 16 ($t = .1$) as are possible with pigs.

The graphs in the figure bring out clearly the almost linear relationship between the genetic gain and the logarithm of the ratio N/T, showing as would be expected, that this ratio and the heritability are the primary factors in determining the extent of the improvement. If we are considering a fixed value of h^2, a decrease in t implies a decrease

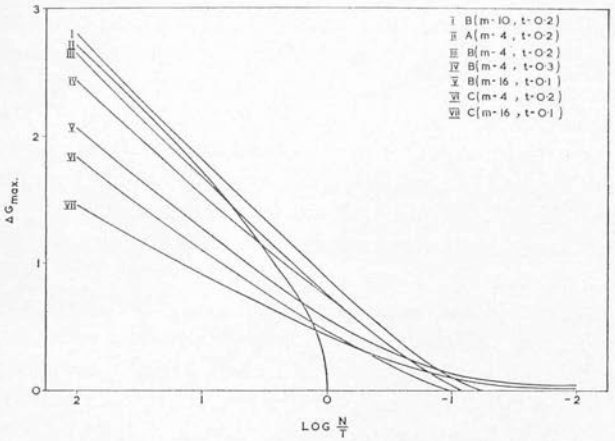

FIGURE 1

THE GENETIC GAINS, IN UNITS OF $h\sigma_G$, FROM TESTING IN THE SPECIFIC CASES LISTED ABOVE AND IN THE TEXT

in the environmental variance common to families and consequently an increase in information per family member tested and an increase in genetic gain as in Graphs III versus IV. As family size increases, fewer families need be selected to supply the breeding requirement. Thus either the choice of families or their accuracy in selection, or both, can be improved giving greater improvement, as in Graphs I versus III. A further relevant comparison concerns the type of family tested. Full-sib families are small but have a higher genetic relationship than half-sib families which in turn are larger. As would be expected, testing full-sib families is superior at high values of N/T where the breeding requirement is small and accuracy in selection is important, and half-sib family testing is preferable at low values of N/T as in Graphs III versus V and VI versus VII. The values ascribed to m, r and t may alter the cross-over points of these graphs appreciably and will determine which testing procedure is desirable for a given ratio of N/T.

We now look at how the improvement is affected by which animals in the selected families are used for breeding. We compare the cases (A) when only tested animals are used, (B) when all members of selected families are used, and (C) when only non-tested members of selected families are used. The advantage of (B) over (C) is to be expected since in (C) we are throwing away the tested animals on which the information is direct besides reducing the numbers available for breeding per family and necessitating the selection of more families. As

tested animals constitute a decreasing part of the total number selected, the actual difference between the (B) and (C) graphs declines, though the relative advantage in terms of the total gains expected may either increase or decrease. Selection of tested animals alone (A) is slightly more efficient than selecting the whole family (B) at high levels of N/T, as in Graphs II versus III, but obviously becomes very inefficient as T approaches N. In general, we may conclude that, if the tested members of the selected families are not used for breeding, the genetic gain will be less than is otherwise possible.

We have considered selection based solely on the family mean, whereas selection will be more effective if based on an index of individual merit and family average. However the discrepancy is not serious. When N/T is small, the outstanding individuals of poor families would form a low proportion of the total number selected and their omission will not affect the improvement by much. On the other hand when N/T is large, accuracy in selection is important and, to obtain this, large fractions of each family are tested. Consequently selecting on an index which includes individual merit will add little to the improvement from selecting on family means.

Changes in the variables may be sought to improve the gains from testing according to the above findings. Unless the breeding requirement is small, changes in the ratio N/T to bring appreciably greater gains may be costly and it may be more expedient to reduce the size of T in some way (see below). The family size and the test group size can be varied at will within the reproductive limits of the species and should be chosen to make the designs efficient.

We have considered selection for a single trait, but in farm animals improvement is generally sought in several traits concurrently. If the various traits can be combined in one statistic, for example the selection index, the above treatment will apply.

IV. THE INTEGRATION OF A TESTING SYSTEM WITH THE POPULATION

We have so far considered only the genetic merit of the selected animals. How should these be used so as the maximise the improvement of the breed or population as a whole from repeated testing? To answer this question we must study the accumulation of improvement from repeated testing and its dissemination throughout the breed.

To study the accumulation of gains from testing we must make some assumptions about the size of the gains in successive generations. Our knowledge of the change in the genetic parameters and response on continued selection in farm animals is scanty. However, where

several traits must be considered concurrently, the selection pressure on any one cannot be very great. Further, the intensity of selection possible is further limited by a slow reproductive rate in farm animals. On these two points it seems reasonable to expect the initial gains to be continued for several generations. With this assumption, it is easy to show that the improvement accumulated after n generations of selecting males is $(n/2)\Delta G$, where ΔG is the gain per generation. If only a fraction q of all sires are selected by testing, the others being selected at random, the improvement will be $(n/2)q\ \Delta G$.

When we come to the dissemination of improvement throughout the breed we are faced with two alternatives. Should the use of the testing facilities and selected animals be restricted to a small section of the breed which can act as a *nucleus* for the supply of breeding stock to the rest of the breeding herds? Or should the facilities and selected animals be unrestricted or *open* to all breeding herds? A nucleus plan is quite feasible in practice with farm animals. A stratified arrangement of breeding operations is clearly defined in many breeds with a flow of breeding stock from few elite herds to the many lower breeding herds. A practical example of a nucleus system is found in the Danish Landrace pig where official testing is restricted to the 250 State breeding centres. The open plan would ignore the presence of breed structure and assume equal use of selected males as sires for the next generation. In practice, this would rarely be the case. Instead, selection will be only partly on test results and disproportionate use is likely to be made of males, selected and unselected, from the elite herds. Unless the elite herds are genetically superior, this practice will reduce the gains possible by the open system proper.

Suppose we employ a nucleus which supplies all the males needed for the other breeding herds. Let us write H_n and M_n for the genetic levels of the nucleus proper and the rest of the breeding herds respectively in the nth generation. Then H_n is equal to $(n/2)\Delta G$. We have $M_{n+1} = \frac{1}{2}(H_n + M_n)$ and substituting for H_n and simplifying, $M_{n+1} = \frac{1}{2}\ \Delta G[n - 1 + (\frac{1}{2})^n]$. If n is large, we can say that the two sections are improving at the same rate and that the rest of the breeding herds lag behind the nucleus by two generations.

When considering the open system, we are concerned with finding whether it is better to supply all the breeding males required even though their average merit will be low, or to supply only a proportion whose average merit will be higher. If we supply a proportion q, the average merit of males used is $q\ \Delta G$. Knowing that ΔG declines as q increases, we wish to know whether there is a maximum for $q\ \Delta G$. It turns out that $q\ \Delta G$ increases continually as q increases so that

the best value of q is one. We should thus provide all the males required in the breeding herds. An exception to this rule is when, to make q equal to one, we have to use animals which are poorer than average. In this case the maximum gains are when all animals which are above average are used though q will be less than one.

Now let us compare the respective merits of the nucleus and open systems. Since the nucleus will require only a fraction of the breeding males which the open system needs, the rate of improvement will be greater in the nucleus. Let us take ΔG_1 as the rate of improvement in the open system and ΔG_2 that in the nucleus system, and $\Delta G_2 > \Delta G_1$. We have shown that ΔG_1 will be proportional to log (N/T), where as before N is the total number of animals tested and T the total requirement for breeding, and ΔG_2 will be proportional to log (Ns/T) where s is the number of breeding sons a sire in the nucleus group supplies to the rest of the breeding herds. That is, the use of a nucleus system will increase the rate of improvement to the same extent as providing s times the original testing facilities. The difference in the rates of gain under the two systems is proportional to log s, and roughly equal, per unit of log s, to the gradient of the plot of ΔG with log (N/T). Some examples of the increased gains possible by the nucleus system can be studied in the figure taking values of s of 10 and 100 say at different levels of N/T. Though the rate of improvement is greater in the nucleus system, there is a two-generation lag between the mean of the nucleus proper and the rest of the breeding herds. Because of this lag, which does not occur in the open system, it may be 4–5 generations before the nucleus plan becomes superior but, because of its greater rate of improvement, it will increase its superiority with each successive generation.

The smaller the nucleus the greater will be the rate of improvement because the smaller will be the requirement of tested animals. However, if the nucleus becomes too small, we come up against the problem of inbreeding. Further, the nucleus should be large enough to supply all the remaining breeding herds with males, unless we have a nucleus within the original nucleus but here again inbreeding would be relevant. We reach the conclusion that the nucleus system of breeding is preferable and the nucleus should be of a size specified by the above provisions and that all testing facilities be entirely devoted to testing animals from the nucleus for future use in the nucleus.

V. SUMMARY

In an extension of Robertson's [1957] work the optimum test design and maximum improvement were studied when selection comprises (*i*)

non-tested members of selected families, (*ii*) all members of selected families, and (*iii*) only tested animals. A variation in considering the breeding requirement as a total of individuals rather than of families was incorporated. Of the three cases the maximum gains are likely to be obtained when all members, tested and untested, of the selected families are used. The total improvement is largely determined by the ratio of the total number tested to the number required for breeding and by the heritability. The efficiency of the test is further affected by the size and nature of the family and by the test group size. These details can be varied to some extent to fit the requirements of efficiency.

Consideration was also given of how best to use the testing facilities and selected individuals, so as to produce the maximum improvement in the breed or population as a whole. Maximum improvement will be obtained if testing facilities are restricted to a nucleus group of breeders, who in turn supply the rest of the breeders with breeding stock, so that full opportunity for testing and selection is confined to the nucleus group.

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Genetic Parameters of British Large White Bacon Pigs

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THE advent of pig progeny testing on a national scale in Britain has made it possible to study the genetic parameters of British pigs tested under carefully controlled conditions with individual feeding. This paper presents estimates of heritabilities and genetic correlations among 35 measurements and scores of Large White pigs. To investigate the inter-relationships of the large number of items studied, a principal component analysis was carried out on the correlation matrices obtained.

MATERIAL AND METHODS

For this analysis data from 494 Large White litter groups tested at the National Progeny Testing Stations during the period from autumn 1957 to spring 1959 were used. Only balanced litter groups of two castrated males (hogs) and two females (gilts) with complete records were included. Pigs entered the stations at 30–45 lb. live-weight, the four pigs comprising the litter group being within a weight range of 8 lb. The pigs were fed individually by hand to appetite, starting the test at 50 lb. live-weight and finishing the test at the first weekly weighing of over 200 lb. live-weight, when they were slaughtered on the following day.

Results were not released to the breeder until four litter groups per sire had been tested, but the data here involved 52 sires with four groups, 40 sires with three groups, 58 sires with two groups and 50 sires with one group. The loss of data from 20 pairs of gilts, due to computer failure, made the distribution of sires and degrees of freedom throughout slightly different for the two sexes. Sexes were analysed separately.

The five stations provided 25, 20, 15, 27 and 13% of the data respectively, and three consecutive six-month periods 25, 32 and 43%. To each pig, 'dummy' variables (0 if absent, 1 if present) were assigned for four stations and two periods (e.g. Quenouille, 1950). The sums of squares and cross-products (S.S.P.) of each source of variation could then be corrected for differences due to stations, periods and last live-weight (all fixed effects) by multiple regression. This is equivalent to the method of fitting additive constants, adjusting the original data by these constants (irrespective of statistical significance) and then analysing the adjusted data. A hierarchical analysis, between sires, between litters within sires, and within litters was performed. The expected mean squares are not changed by adjusting the data for fixed effects.

The work was done by the Elliott-N.R.D.C. 401 computer at Rothamsted.

Three programmes were written, one using ordinary arithmetic for between and within-litter S.S.P., one using floating point arithmetic for (weighted) between-sires S.S.P. and one, floating point, for matrix addition, scalar multiplication and elimination by regression of 'dummy' variables for seasons and stations. The first programme, when accumulating between litters S.S.P., subtracted working means from the observations to avoid overflow and to maintain accuracy, and punched out the means for each sire on tape. This tape was then used as a data tape for the between-sires S.S.P. Various data-reading and numerical checks were employed. The floating point arithmetic works to about seven decimal places, so that the final results are arithmetically correct to at least three decimal places.

The distribution of additive genetic variance among the various components of variation was calculated in the manner described by Dickerson (1947). The genetic relationships (Wright, 1922) required were obtained from a slightly different sample of 60 sires, all with four litter groups tested. The average relationship between sows mated to one sire was 0·096 and between a sire and his mates 0·042. The expected mean squares and the composition of the components of variance and covariance are:

	d.f.	Expected mean squares	Composition of components
Between sires	199	$\sigma_1^2+2\sigma_2^2+4{\cdot}935\sigma_3^2$	$\sigma_3^2 = 0{\cdot}295\sigma_G^2$
Between litters within sires	288	$\sigma_1^2+2\sigma_2^2$	$\sigma_2^2 = 0{\cdot}226\sigma_G^2+\sigma_L^2$
Within litters	493	σ_1^2	$\sigma_1^2 = \sigma_E^2+0{\cdot}479\sigma_G^2$

where σ_G^2, σ_L^2 and σ_E^2 represent respectively the additive genetic, non-genetic litter, and residual variances and covariance components. The sire component will in fact estimate the strictly additive genetic variance plus a contribution, assumed negligible, made up of a small fraction of the interaction between loci involving additive effects (e.g. Kempthorne, 1955). Another assumption is that the effect of farm environment on pigs coming from different farms is negligible. If this is not the case, use of the sire component will lead to an overestimate of heritability, and this reservation has to be borne in mind.

A litter component of variation is made up of environmental influences common to the litter as a whole, but as estimated will also contain some non-additive genetic effects, principally those due to dominance (Kempthorne, 1955).

Approximate standard errors were calculated for the portions of the variance due to genetic effects and to litter effects (Woolf, 1960, personal communication) and standard errors of the genetic correlations by the method of Tallis (1959).

The pattern of correlations obtained for both genetical and residual (environmental) effects were examined by principal component analysis (cf. Kendall, 1957). The latent roots and vectors required were obtained with a standard computer programme.

Complete records were available for each pig on the following 35 measures and scores. For the location of some measures see Figure 1.

Daily gain on test—the average daily weight increment over the test period.

Food conversion (live-weight)—the total food eaten on test/total live-weight gain.

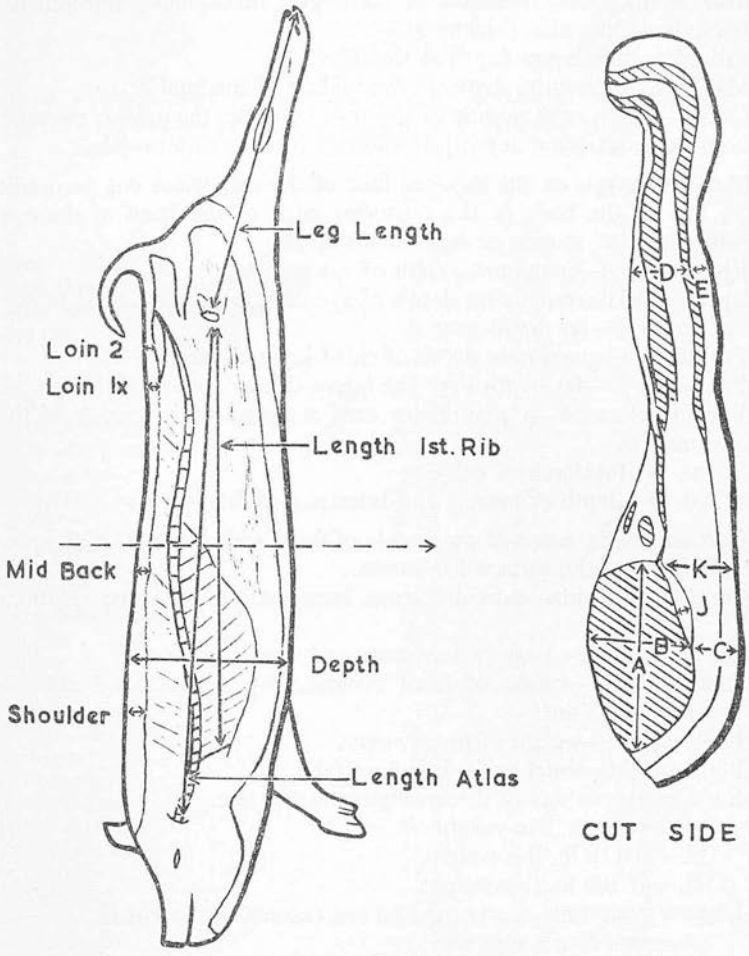

FIG. 1. Pig carcass showing the location of the carcass measurements.

Food conversion (dead weight)—the total food eaten on test/total dead weight gain, the latter taken as carcass weight minus an estimated initial carcass weight of 30 lb.

Last live-weight.

Dressing out %—the carcass weight as % of last live-weight.

Length to 1st rib—taken on the warm suspended carcass, from the *symphysis pubis* to the anterior edge of the first rib.

Length to atlas—taken on the cold horizontal carcass from the *symphysis pubis* to the atlas joint.

Vertebra number—lumbar plus thoracic.

Carcass depth—maximum depth from the sternum to the back.

Leg length—from the tip of the toe to the anterior edge of the *symphysis pubis*.

Loin length—from the anterior edge of the *symphysis pubis* to the posterior edge of the last rib.

Backfat thickness, measures of fat depth, taken along the mid line of the back (including skin thickness).

Shoulder—maximum depth at shoulder.

Mid-back—minimum depth in the middle of the back.

Loin 2—depth over middle of the rump muscle, the *gluteus medius*.

Loin 1x—maximum depth just anterior to the rump muscle.

Measures taken on the exposed face of the side when cut perpendicular to the line of the back at the posterior edge of the head of the last rib, exposing the 'eye' muscle or *longissimus dorsi*.

Eye muscle A—maximum width of eye muscle.

Eye muscle B—maximum depth of eye muscle perpendicular to A.

Fat depth C—fat depth over B.

Fat depth J—maximum depth of third layer of fat.

Fat depth K—fat depth over the latero-dorsal corner of the eye muscle.

Eye muscle area—a planimeter area measure of a tracing of the eye muscle.

Streak E—fat depth of belly.

Streak D—depth of muscle and interspersed fat over E.

Carcass scores, assessed on a scale of 0–50 with intervals of 5, indicating the suitability of the carcass for bacon.

On the uncut side—shoulder score, ham score and carcass conformation score.

On the cut side—back rasher score and streak score.

Head weight—weight of head removed by a horizontal cut through the atlas joint.

Fillet weight—weight of *psoas major*.

Flare weight—weight of warm flare fat.

Food eaten per day at three weights during test.

I.—at 50 lb. live-weight.

II.—at 125 lb. live-weight.

III.—at 200 lb. live-weight.

Disease symptoms at any time on test (absent 0, present 1).

1.—scouring symptoms.

2.—'thumping' (symptom of lung disease).

RESULTS

The means of the 35 measures and scores for each sex and their overall standard deviations, corrected for differences between stations, season and in last live-weight, are given in Table 1. In general, the gilts were better bacon pigs, being more efficient, not so fat and with higher muscle and carcass scores. The gilts were also slightly less variable than the hogs. Body measures such as carcass length had low coefficients of variation (2–4%), growth, efficiency and food eaten had coefficients around 6–10%, measures of fat depth and muscle depth from 10–20%, while the various carcass scores had coefficients of variation from 15–30%.

The total variation was partitioned into additive genetic variance, non-genetic litter variance and residual variance. Approximate standard errors were attached to these portions. There was good agreement between the sexes in the various estimates; only one trait showed a significant difference between sexes for the additive genetic variance, and three traits for the litter

TABLE 1

Means of 35 traits, and their overall standard deviations after correction for differences in stations, seasons and slaughter weight

	Hogs		Gilts	
	Mean	S.D.	Mean	S.D.
Daily gain (lb./day)	1·52	0·14	1·51	0·12
Food con. (live-wt.) (lb. food/lb. gain)	3·41	0·24	3·31	0·23
Food con. (dead wt.) (lb. food/lb. carc. gain)	4·37	0·29	4·22	0·28
Dressing out %	73·5	1·69	73·9	1·62
Food I. (lb. food/day)	2·35	0·26	2·37	0·26
Food II (lb. food/day)	6·52	0·42	6·24	0·46
Food III (lb. food/day)	7·59	0·50	7·23	0·53
Length to 1st rib (mm.)	802·2	19·6	809·7	20·0
Length to atlas (mm.)	931·3	22·5	938·1	23·6
Vertebra number	21·4	0·55	21·4	0·54
Carcass depth (mm.)	323·5	8·9	324·2	9·5
Leg length (mm.)	604·3	15·1	605·3	15·2
Loin length (mm.)	363·9	15·9	369·4	16·9
Head weight (lb.)	19·41	1·19	19·65	1·12
Backfat shoulder (mm.)	46·9	4·61	44·1	4·28
Backfat mid-back (mm.)	21·8	3·62	18·6	3·02
Backfat loin 2 (mm.)	28·1	4·60	23·8	4·23
Backfat loin 1x (mm.)	33·3	4·24	30·1	4·05
Fat depth C (mm.)	23·1	4·41	18·1	3·42
Fat depth J (mm.)	6·47	2·44	3·89	2·16
Fat depth K (mm.)	30·1	5·01	23·5	4·14
Streak E (mm.)	8·96	1·97	7·88	1·71
Flare weight (lb.)	4·36	0·95	3·88	0·86
Eye muscle A (mm.)	74·1	4·66	78·9	4·90
Eye muscle B (mm.)	44·8	4·54	48·6	4·34
Eye muscle area (sq. cm.)	24·69	3·13	28·09	3·16
Streak D (mm.)	22·5	3·02	21·9	2·96
Fillet weight (lb.)	1·78	0·19	1·92	0·19
Shoulder score (points)	24·5	9·16	24·2	9·24
Ham score (points)	25·6	7·17	28·8	6·93
Back rasher score (points)	23·9	10·50	38·9	7·75
Streak score (points)	31·9	5·81	31·9	5·37
Carcass conformation score (points)	21·8	8·98	23·6	9·13
Disease 1	0·25	0·61	0·19	0·55
Disease 2	0·14	0·50	0·16	0·51

differences. Since at this level of probability ($P = 0{\cdot}05$) as many differences as these are expected by chance alone, they can be dismissed and the estimates for each sex pooled. The pooled estimates are presented in Table 2 together with their approximate standard errors. The additive genetic portion was significant in all but one trait and contributed from 0·14 to 0·78 of the total variation in different traits. The litter variance contributed considerably less (0–0·28) of the total variation and was significant for only 11 traits. Of these, five were associated with gain and

food eaten on test, suggesting that common litter environment had so influence on traits measured during life, but had little carry-over effect i carcass traits.

TABLE 2

Proportions of the variance attributed to different causes and their approximate standard errors

	Additive genetic variance (heritability)	S.E.	Litter variance	S.E.	Residu varian
Daily gain	0·41	0·099	0·15	0·053	0·44
Food conversion (live-wt.)	0·50	0·098	0·14	0·051	0·36
Food conversion (dead wt.)	0·58	0·101	0·14	0·051	0·28
Dressing out %	0·40	0·091	0·09	0·049	0·51
Food I	0·26	0·090	0·18	0·051	0·56
Food II	0·66	0·099	0·07	0·050	0·27
Food III	0·34	0·100	0·28	0·054	0·38
Length to 1st rib	0·60	0·101	0·12	0·051	0·28
Length to atlas	0·78	0·102	0·04	0·049	0·18
Vertebra number	0·35	0·093	0·07	0·050	0·58
Carcass depth	0·34	0·087	0·08	0·049	0·58
Leg length	0·50	0·094	0·08	0·050	0·42
Loin length	0·46	0·093	0·08	0·049	0·46
Head weight	0·49	0·096	0·10	0·050	0·41
Backfat shoulder	0·62	0·101	0·09	0·050	0·29
Backfat mid-back	0·73	0·097	0·00†	0·047	0·27
Backfat loin 2	0·71	0·100	0·05	0·049	0·24
Backfat loin 1x	0·68	0·097	0·01	0·048	0·31
Fat depth C	0·65	0·096	0·02	0·048	0·33
Fat depth J	0·64	0·093	0·00†	0·046	0·36
Fat depth K	0·73	0·099	0·00†	0·048	0·27
Streak E	0·29	0·089	0·15	0·051	0·56
Flare weight	0·61	0·094	0·00	0·048	0·39
Eye muscle A	0·46	0·091	0·05	0·049	0·49
Eye muscle B	0·48	0·091	0·04	0·048	0·48
Eye muscle area	0·35	0·088	0·07	0·050	0·58
Streak D	0·24	0·085	0·11	0·049	0·65
Fillet weight	0·31	0·088	0·11	0·051	0·58
Shoulder score	0·25	0·083	0·08	0·049	0·67
Ham score	0·35	0·090	0·11	0·051	0·54
Back rasher score	0·59	0·097	0·06	0·049	0·35
Streak score	0·32	0·086	0·08	0·049	0·60
Carcass conformation score	0·31	0·086	0·09	0·050	0·60
Disease 1	0·25	0·084	0·09	0·046	0·66
Disease 2	0·14	0·109	0·11	0·062	0·75

† Negative components—none significant.

The 35 traits fell into several broad categories measuring fat dep and fatness, muscling, body dimensions and so on, and it is convenient consider these groups rather than the individual traits. Looking at t additive genetic portion of the total variation, that is the heritability, general description is possible. The estimates of heritability of measu of fat depth ranged from 0·6 to 0·8, of muscling measures from 0·3 to 0 of carcass scores around 0·3 except for back-rasher score at 0·6, of bo

length from 0·5 to 0·8, and of measures of daily gain and food eaten on test from 0·3 to 0·6. The ranking of these categories and their general levels of heritability agree fairly well with other published results.

The *phenotypic* correlations, estimated from the total variances and covariances were very similar in the two sexes and their average is given in Table 3, each correlation having a standard error of about 0·02. The *genetic* correlations were estimated from the sire components of variance and covariance and have larger sampling errors. A number of specimen standard errors were calculated following Tallis (1959); these were all about 0·2. The agreement between the two sexes for these genetic correlations is therefore not expected to be as close as for the phenotypic correlations. Over the table as a whole the two sexes showed a similar pattern of correlations, although many differences were significant. Only analysis of further data can show whether these differences are real. The genetic correlations for the two sexes combined are given in Table 3. The phenotypic and genetic correlations behave similarly. The genetic correlations are, with few exceptions, of the same sign and of a higher absolute value than the phenotypic correlations.

It is hard to summarise these 1056 correlations in other than general terms. It is the biological meaning of the correlation coefficients, the implications of the degree and sign of relationship, which matters rather than the statistical significance. The first impression from the table is of high phenotypic and genetic correlations among traits concerned with one particular aspect of the pig. Measures of fat depth at several locations on the carcass are highly correlated, and so too are measures of food efficiency, measures of length, certain scores, appetite and to a lesser extent measures of muscling. One trait in each of these groups is probably sufficient to represent the whole group. The phenotypic and genetic correlations between traits of different categories are of a lower order and frequently not significant. There is a general high negative relationship of fat depth with measures of muscling and with carcass scores which are positively intercorrelated. The measures of length tend to be positively correlated with measures of muscling and some carcass scores but negatively correlated with fat depth, and the reverse holds for carcass depth. Daily gain and food conversion show quite a high negative correlation with each other, but differ in their associations with other groups of traits, in particular with muscle measures and daily food intake. Food conversion and daily food intake tend to be correlated positively with fat depth and negatively with measures of muscling and carcass scores. Among all 33 traits, head weight seems to be least dependent on the others.

Principal component analysis

This technique attempts to summarise all the correlations between a number of variates by expressing them in terms of a lesser number of new variates, called components, which are linear functions of the original variates. (These 'components' should be carefully distinguished from the 'components of variance' arising in the analysis of variance.) The first component is chosen so as to account for as much of the correlation pattern as possible. The second component is chosen to be uncorrelated with the first and to account for as much of the residual correlation pattern as possible, and similarly for successive components. It will usually take as many

TABLE 3

Phenotypic correlations (above the diagonal) and genetic correlations (below) among 33 traits

	Daily gain	Food con. (live wt.)	Food con. (dead wt.)	Dressing out %	Food I	Food II	Food III	Length to 1st rib	Length to atlas	Vertebra number	Carcass depth	Leg length	Loin length	Head weight	Backfat shoulder	Backfat mid-back	Backfat loin 2	Backfat 1x	Fat depth C	Fat depth J	Fat depth K	Streak E	Flare weight	Eye muscle A	Eye muscle B	Eye muscle area	Streak D	Fillet weight	Shoulder score	Ham score	Back rasher score	Streak score	Carc. conform. score
Daily gain		−·66	−·57	−·27	·10	·45	·46	·13	·05	−·01	−·20	−·08	·01	−·05	·00	·00	·01	·02	−·06	−·04	·04	−·21	−·16	−·06	·04	·02	−·17	−·03	·18	·08	·06	−·15	·19
Food con. (live wt.)	−·69		·91	·31	·09	·04	−·06	−·16	−·06	·01	·28	−·03	−·07	·04	·19	·19	·24	·19	·24	·16	·24	·23	·27	−·03	−·14	−·11	·19	−·10	−·26	−·05	−·27	·23	−·27
Food con. (dead wt.)	−·60	·94		−·08	·06	·06	−·01	−·09	−·01	·01	·18	−·04	−·04	−·03	·12	·09	·19	·10	·18	·12	·19	·15	·19	−·10	−·24	−·21	·07	−·17	−·16	−·13	−·24	·08	−·20
Dressing out %	−·24	·13	−·23		·07	−·05	−·15	−·20	·01	·01	·25	·02	−·07	·16	·18	·25	·14	·23	·16	·10	·12	·20	·23	·15	·23	·22	·28	·16	−·24	·16	−·10	·38	−·19
Food I	·40	·10	·07	·09		·04	·04	·01	−·01	·02	·06	−·07	−·03	·05	·08	·06	·06	·07	·00	·02	·03	·06	·06	·00	·05	·03	·03	−·02	−·05	·02	−·03	·05	−·04
Food II	·41	·25	·18	·16	·37		·64	·00	·00	·05	·03	·17	−·05	−·03	·20	·15	·25	·20	·17	·14	·26	·09	·09	−·14	−·07	−·10	−·04	−·13	−·03	·02	−·20	·00	·00
Food III	·32	·18	·21	−·12	·36	·89		·00	−·05	·00	·02	−·17	−·02	−·04	·20	·19	·27	·24	·22	·19	·28	·08	·05	−·19	−·10	−·13	−·10	−·15	·00	·02	−·22	−·07	−·02
Length to 1st rib	·19	−·25	−·19	−·25	−·14	·00	−·16		·79	·32	−·33	·17	·22	·00	−·18	−·22	−·18	−·19	−·23	−·19	−·24	−·21	−·19	−·05	−·04	−·04	−·21	−·03	·45	−·13	·25	−·28	·52
Length to atlas	−·17	·00	·02	−·07	−·34	·05	−·16	·82		·34	−·21	·35	·30	·00	−·19	−·30	−·22	−·26	−·24	−·19	−·26	−·15	−·14	·02	−·10	−·05	−·18	−·02	·32	−·22	·24	−·26	·35
Vertebra number	−·37	·37	·37	−·03	·23	−·02	·06	·28	·37		−·03	−·02	−·18	·01	−·01	−·12	−·06	−·10	−·13	−·08	−·09	−·03	−·06	−·04	·09	·06	−·06	−·03	·11	·07	·13	−·08	·16
Carcass depth	−·39	·61	·60	·00	·08	·16	·28	−·60	−·37	·12		·01	−·03	·04	·26	·15	·15	·14	·16	·16	·14	·14	·16	·05	−·03	−·01	·15	·00	−·76	−·11	−·15	·21	−·67
Leg length	−·16	−·07	·00	−·18	−·52	−·05	−·24	·22	·50	−·06	−·48		·23	·12	−·27	−·34	−·32	−·33	−·27	−·19	−·32	−·18	−·18	·14	−·04	·05	−·05	·08	·02	−·32	·27	−·11	·01
Loin length	·04	−·15	−·12	−·06	−·16	·09	−·15	·37	·55	·21	−·12	·41		·04	−·10	−·11	−·08	−·09	−·10	−·12	−·23	−·06	·01	·04	−·15	−·07	·02	·00	·11	−·17	·05	−·03	·08
Head weight	·00	·04	−·03	·19	·12	·16	·10	·03	·09	−·07	−·02	·11	·09		−·03	−·12	−·11	−·11	−·15	−·14	−·15	·00	−·24	·05	·04	·01	−·03	·04	−·05	−·05	·14	−·05	−·03
Backfat shoulder	−·04	·26	·17	·24	·20	·33	·44	−·32	−·27	·02	·39	−·59	−·25	−·14		·52	·49	·51	·41	·26	·44	·26	·23	−·21	−·06	−·13	·07	−·14	−·25	−·02	−·38	·12	−·26
Backfat mid-back	·13	·02	−·07	·20	·34	·21	·40	−·29	−·42	−·41	·19	−·56	−·12	−·11	·78		·60	·70	·60	·39	·58	·28	·30	−·16	·01	−·04	·10	−·12	−·14	·06	−·50	·18	−·16
Backfat loin 2	−·01	·33	·27	·10	·15	·38	·37	−·42	−·40	−·31	·39	−·44	−·10	·00	·80	·73		·78	·63	·40	·61	·29	·34	−·30	−·17	−·22	·02	−·19	−·14	−·04	−·56	·10	−·18
Backfat loin 1 x	·01	·15	·03	·28	·16	·30	·32	−·37	−·41	− ·24	·24	−·50	−·11	−·10	·79	·90	·83		·63	·41	·62	·29	·33	−·25	−·05	−·12	·08	−·18	−·12	−·03	−·53	·15	−·15
Fat depth C	·04	·15	·12	·07	−·13	·37	·53	−·33	−·37	−·29	·26	−·36	−·23	−·20	·71	·75	·73	·78		·63	·79	·38	·40	−·39	−·31	−·33	·08	−·20	−·17	−·07	−·73	·13	−·22
Fat depth J	·08	−·03	−·02	−·03	−·01	·09	·37	−·22	−·36	−·23	·22	−·38	−·23	−·30	·62	·64	·43	·65	·86		·56	·23	·38	−·31	−·20	−·30	·10	−·20	−·15	−·04	−·58	·11	−·19
Fat depth K	−·02	·24	·19	·11	·01	·44	·51	−·35	−·44	−·26	·28	−·40	−·18	−·13	·66	·81	·68	·79	·87	·77		·35	·38	−·40	−·20	−·29	·06	−·20	−·16	−·03	−·77	·10	−·19
Streak E	·61	·26	·20	·18	·31	·43	·68	−·08	·10	·13	·52	−·06	·08	−·25	·43	·19	·26	·21	·09	·10	·21		·19	−·10	−·08	−·08	·24	−·07	−·13	·00	−·31	·32	−·14
Flare weight	−·33	·31	·22	·24	−·04	−·06	·01	−·22	−·22	−·09	·07	−·22	·10	−·25	·49	·39	·48	·49	·45	·52	·43	·23		−·20	−·12	−·18	·15	−·05	−·16	−·06	−·41	·18	−·19
Eye muscle A	−·29	−·01	−·07	·15	·01	−·39	−·70	·11	·37	·05	·13	·45	·26	−·03	−·72	−·50	−·57	−·54	−·64	−·46	−·62	−·03	−·37		·31	·54	·13	·24	−·04	·19	·45	·15	·00
Eye muscle B	−·16	−·25	−·39	·38	·25	−·34	·65	·02	·04	·43	−·11	−·14	−·15	·11	−·11	−·09	−·37	−·24	−·50	−·38	−·34	−·05	−·27	·43		·61	·08	·19	·05	·24	·36	·11	·11
Eye muscle area	−·38	−·15	−·34	·47	·03	−·52	−·86	·08	·31	·32	·02	·15	·29	·12	−·42	−·27	−·42	−·26	−·58	−·35	−·48	−·02	−·23	·79	·82		·10	·25	·02	·22	·38	·15	·07
Streak D	−·20	·07	−·05	·37	·26	−·01	−·30	−·49	−·42	·22	·29	−·10	−·26	−·07	−·05	−·02	−·20	−·05	−·12	·11	·15	−·15	·07	·04	·13	−·11		·03	−·14	·07	−·08	·61	−·15
Fillet weight	·13	−·34	−·31	−·06	−·13	−·33	−·35	−·03	−·05	·11	−·02	−·10	·10	−·08	−·35	−·28	−·03	−·25	−·26	−·23	−·21	−·20	·00	·34	·10	·26	−·51		−·04	·06	·24	·04	·00
Shoulder score	·27	−·57	−·52	−·17	−·39	−·13	−·34	·64	·50	−·17	−·97	·52	·35	·02	−·50	−·26	−·51	−·38	−·45	−·24	−·39	−·40	−·09	·11	·09	·11	−·23	−·36		·13	·16	−·20	·87
Ham score	·09	−·33	−·38	·09	·49	−·05	−·20	−·16	−·18	·08	·20	−·24	−·27	·07	−·03	−·01	−·23	−·11	−·17	−·11	−·13	·07	−·18	·35	·60	·50	−·22	·24	−·14		·08	·13	·21
Back rasher score	·09	−·30	−·26	−·04	·03	−·27	−·45	·43	·49	·37	·27	−·40	−·32	−·22	−·65	−·79	−·74	−·83	−·93	−·79	−·97	−·25	−·54	·66	·41	·49	−·11	·29	−·36	·18		−·08	·28
Streak score	−·21	·19	·02	−·09	·09	·02	·29	−·24	−·23	·12	·45	·17	·18	·29	−·02	−·08	−·13	−·00	−·15	−·02	−·09	−·15	−·14	·24	·25	·14	−·08	·15	·14	·22	·33		
Carc. conform. score																																	

components as original variates to account for all the original correlation pattern. The objective is to represent the correlation pattern adequately by the first few components and to concentrate attention on these while neglecting the remainder. A measure of what part of the total pattern each component describes is given by its latent root, which is in fact the variance of that component.

The 'genetic' and 'environmental' correlations observed among 24 of the more important variates were chosen for principal component analysis.

TABLE 4

Vectors and latent roots of the first two principal components (I and II) of the genetic and environmental correlation matrices

	Genetic matrix		Environmental matrix	
	I	II	I	II
1. Daily gain	−0·03	0·24	−0·09	0·28
2. Food conversion (dead wt.)	0·11	−0·16	0·22	−0·11
3. Dressing out %	0·06	−0·19	0·14	−0·29
4. Length to 1st rib	−0·18	0·29	0·08	0·24
5. Carcass depth	0·18	−0·38	0·00	−0·40
6. Leg length	−0·18	0·03	−0·19	−0·21
7. Backfat shoulder	0·30	0·04	0·05	−0·05
8. Backfat mid-back	0·28	0·10	0·23	−0·06
9. Backfat loin 2	0·29	0·05	0·32	0·14
10. Backfat loin 1x	0·30	0·09	0·29	0·07
11. Fat depth C	0·30	0·14	0·39	−0·01
12. Fat depth J	0·25	0·14	0·22	−0·04
13. Fat depth K	0·30	0·08	0·35	0·05
14. Streak E	0·11	−0·07	0·32	−0·11
15. Flare weight	0·19	0·04	0·20	−0·14
16. Eye muscle A	−0·22	−0·25	−0·09	−0·13
17. Eye muscle B	−0·13	−0·19	−0·05	−0·04
18. Streak D	0·04	−0·30	0·13	−0·15
19. Fillet weight	−0·07	−0·09	−0·09	−0·11
20. Shoulder score	−0·21	0·34	0·06	0·43
21. Ham score	−0·05	−0·21	0·10	0·16
22. Back rasher score	−0·31	−0·09	−0·28	−0·02
23. Streak score	0·03	−0·37	0·20	−0·18
24. Carcass conformation score	−0·20	0·28	0·06	0·43
Latent root	8·63	3·83	4·22	3·40

Correlations, rather than covariances, were used since the scales of measurement of the different variates are not comparable. While the sum of the latent roots of the 24 components is 24 in each case, the first two latent roots add up to 12·46 and 7·62 for the genetic and environmental correlation matrices respectively. The third and fourth latent roots add up to 4·86 and 4·00 for the two matrices respectively, and the other roots are comparatively unimportant. The first two components here give a reasonable approximation to the correlation pattern. Attention can be concentrated on these two components, so simplifying the problem of assimilating a mass of correlation coefficients.

In the matrix of genetic correlations 6 of the 24 latent roots turned out

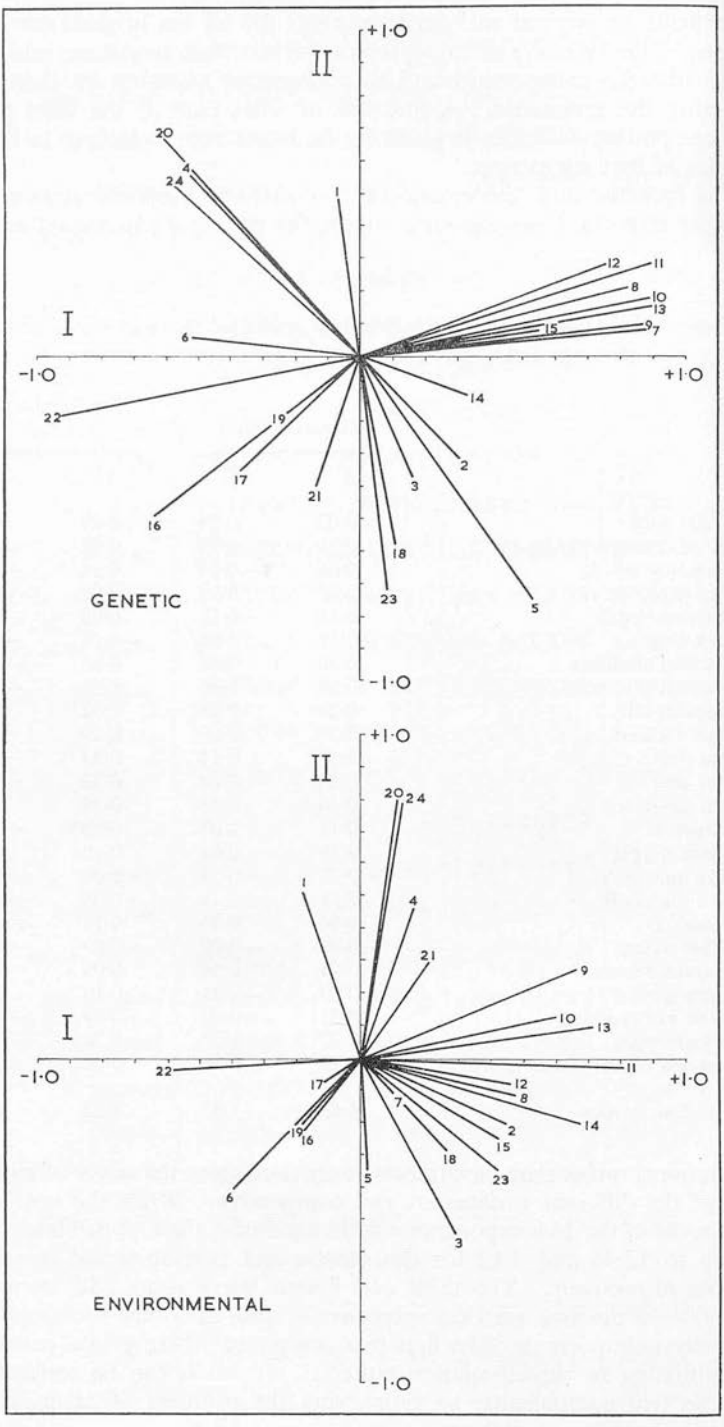

FIG. 2. Diagram of the vectors of the first two components (I and II) of the genetic and environmental correlation matrices. (Numbers on vectors refer to traits listed in Table 4.)

to be negative. This would be impossible in an ordinary correlation matrix, but in a derived matrix could be due to a variety of causes, e.g. sampling errors in the components of variance and covariance, or a failure of the assumptions made in the interpretation of these components. The principal components analysis may have the virtue of extracting two reliable variates from a mass of correlation coefficients which individually are of doubtful reliability.

The first two latent roots and their vectors for the genetic and environmental correlation matrices are given in Table 4. The vector coefficients for the genetic and environmental cases are seen to be in good agreement for the first two principal components. This means that the major genetic and major environmental relations between the traits considered are similar. The first principal component of the genetic correlation matrix has high positive vector coefficients for measures of fat depth and high negative vector coefficients for back rasher score, shoulder score, carcass conformation score, length and eye muscle depth and width. The first component could therefore be interpreted as some function of fatness which is negatively associated with measures of carcass desirability, muscle measures and length. The second principal component has high positive vector coefficients for length, carcass conformation score, shoulder score and daily gain and high negative vector coefficients for carcass depth, streak D and streak score, ham score, eye muscle width and % dressed carcass. Thus it appears to be associated with carcass dimensions, that is length and depth, and reflects greater muscle measurements both in the eye muscle and streak.

A visual representation of the first two principal components helps to summarise the information which the analysis provides about the correlation matrix. In the figure (Figure 2) the vector of the first two components of the genetic and environmental correlation matrices have been plotted and the points joined to the origin. To reflect the relative importance of the two components in explaining the correlation pattern, the vectors have been multiplied by the square root of the latent root and plotted on a common scale. Traits whose lines are close together will be similar in nature, those with lines at right angles to each other will be independent, and those with lines diametrically opposed are equivalent in that they measure the same quantity but differ in sign. It must be emphasised again that the first two vectors merely approximate the actual correlations which are set out in Table 3, so that the spatial arrangement in the figure accounts for only some part of the relations among traits.

In the genetic analysis the 8 measurements of fat depth (Nos. 12, 11, 8, 10, 13, 15, 9 and 7) are compactly grouped, showing that these measurements are measuring very much the same thing and in addition that back rasher score (No. 22) can be regarded as essentially a negative measure of fat depth. Eye muscle width (No. 16) and eye muscle depth (No. 17) and fillet weight (No. 19) lie together and are negatively associated with fat depth. Shoulder score (No. 20) and carcass conformation score (No. 24) are, apparently, largely determined by the length of the carcass (No. 4) and are opposite to carcass depth (No. 5). Streak score (No. 23) is close to the measurement of muscle in streak D (No. 18) and removed from the measure of streak fat (streak E, No. 14) which shows a closer affinity to other fat measurements. The expected relationships between daily gain (No. 1), food conversion (dead weight) (No. 2) and dressing out % (No. 3) can be seen although

the short radii shown on this figure indicates that the correlations explained by these first two principal components are not high.

The figure of components for the environmental correlation matrix is broadly similar to the genetic one but individual traits are more dispersed and do not show the same close associations. There also appears to have been a rotation of the axis of the diagram, but without any fundamental change in relationships.

DISCUSSION

The practical significance of the estimated genetic parameters lies in the prediction of improvement through selection. The expected genetic change in a population through selection is determined by the heritability of each trait, the selection differential applied and the genetic correlation among the characters under study.

The traits most commonly investigated in pigs have been daily gain, food conversion, backfat thickness and carcass length. A resumé of the estimates of the heritabilities for these traits calculated from progeny testing station records is given in Table 5.

TABLE 5

A summary of the heritabilities of four traits estimated from progeny testing station records

	Group feeding					Individual feeding		
	1	2	3	4	5	6	7	8
Daily gain	0·24	—	0·25	0·21	0·15	0·50	0·44	0·41
Food conversion	—	0·30	0·18	—	—	0·58	0·44	0·50
Carcass length	0·47	0·40	0·61	0·66	0·39	0·48	0·45	0·60
Backfat thickness	0·54	0·43	0·54	0·48	0·43	0·55	0·47	0·66

(1) Lush (1936). Danish Landrace, 83 sires.
(2) Fredeen (1953). Canadian Yorkshire, 644 sires.
(3) Johansson and Korkman (1950). Swedish Landrace, 1693 sires.
(4) Osterhoff (1956). Swedish Landrace, 640 sires.
(5) Broderick (1960). Irish Large White, 60 sires.
(6) Fredeen and Jonsson (1957). Danish Landrace, 468 sires.
(7) Jonsson and King (1962). Danish Landrace, 935 sires.
(8) Smith, King and Gilbert (here). British Large White, 200 sires.

There is no basic necessity for the estimates of heritability relating to various populations and environments to agree. In view of the sampling errors and the various biases to which they are liable, there is good agreement in the estimates of heritability of backfat thickness and carcass length among the different authors, and good agreement within feeding regime for daily gain and food conversion. The different degree of heritability, however, for these two latter traits in the two sexes found by Fredeen and Jonsson (1957) was not apparent here. Jonsson (1959) compared the variation among group-fed and individually-fed pigs and found that the higher estimates of heritability of daily gain in the latter arose largely from the reduction of the intra-test-group (intra-litter) component, and ascribed this reduction to the elimination of intra-litter competition when pigs are

individually fed. In agreement with the estimates of Fredeen (1953) and Jonsson and King (1962) heritabilities of visual scores of carcass suitability such as ham score, shoulder score and carcass scores tended to be less than the heritabilities of measurements of carcass desirability especially fat depth and carcass length. Few estimates of the heritability of eye muscle measurements appear in the literature. An estimate of 0·66 for eye muscle area reported by Fredeen (1953) and one of 0·29 for eye muscle depth by King (1957) may be compared respectively with the estimates 0·35 and 0·48 reported here.

Analyses of testing station records have been a common means of investigating the genetic parameters of pig populations but this type of data may be somewhat artificial. Pigs entering a testing station are usually of selected parents, of a uniform weight and conform to the ideals of the breeder. The progeny of a sire experience the same pre-test farm environment, the effect of which may not be insignificant (Lauprecht and Walter, 1960; Broderick, 1960; Jonsson and King, 1962), and tend to be contemporary at the station. Breeders may favour different ideals or some may be more successful than others so that dissimilar strains exist. On the other hand only those breeders with a common goal may enter into progeny testing. These factors, if they are relevant, may affect the estimates of heritability in testing station data and should be borne in mind in interpreting and applying the estimates of genetic parameters in practice.

The selection differential for any one trait will be determined by the emphasis it receives when breeders make their selections, and by the choice available among breeding animals. Of the breeders who progeny-tested Large White boars in Britain in 1960 only 25% tested more than one boar per year so that within herds the choice among boars tested at the stations is very limited. On the other hand the individual breeder may choose from the total of 141 boars tested. A strong demand for progeny of high-ranking boars indicates that this type of selection is common. The selection differential depends not only on the intensity of selection but also on the observed variability of the trait. That different degrees of variability may exist in different pig populations is brought out by comparing Danish Landrace (Jonsson and King, 1962) and British Large White pigs all fed individually at testing stations. The standard deviations, averaged over the two sexes, for four traits are given below.

	British Large White (1)	Danish Landrace (2)
Daily gain (lb./day)	0·13	0·07
Live food conversion (lb. food/lb. gain)	0·23	0·14
Length to atlas (mm.)	23·0	20·0
Backfat thickness (mm.)	3·38	2·94

(1) Smith, King and Gilbert (here).
(2) Jonsson and King (1962).

British Large Whites are about twice as variable as Danish Landrace for daily gain and food conversion and are also more variable for backfat thickness and carcass length, though the latter two are not quite identical measurements in the two populations. Because of this higher degree of variability with effectively the same heritabilities, a greater rate of improvement should be possible (with the same intensity of selection) in British

than in Danish pigs. Referring back to the work of Jonsson (1959) in comparing the variation and heritability of individually- and group-fed pigs the higher heritability of daily gain noted in the former must be set against the concurrent reduction in variation. Because the selection differential, with the same intensity of selection, will be less, the genetic improvement on individual feeding may not be greatly increased in spite of the higher heritability. It is interesting to speculate on why different levels of variability exist in the Danish Landrace and British Large White. The lower variability of the Danish Landrace may be due to the effects of long term selection in improving these traits as illustrated by Clausen and Nørtoft Thomsen (1961) for backfat thickness. The difference may also be partly due to the different feeding systems employed.

By selection for one or several traits the breeder indirectly exerts selection pressure on other traits. The value of his selections may be nullified if

TABLE 6

Expected response from one generation of selection for various traits when the best 25% of boars tested are used

Selection for improvement in	Daily gain (lb./day)	Food conversion (dead wt.) (lb. food/ lb. carcass	Average backfat (mm.)	Length (mm.)	Eye muscle area (cm^2)	Carcass conformation (points)
Daily gain	0·039	−0·06	−0·05	1·4	−0·34	0·8
Food conversion (dead wt.)	0·025	−0·12	−0·41	1·5	0·33	1·4
Average backfat	0·001	−0·03	−1·84	3·3	0·46	1·5
Length	0·007	−0·02	−0·68	7·9	0·08	1·7
Eye muscle area	−0·014	−0·04	−0·72	0·6	0·88	0·5
Carcass conformation	0·012	−0·05	−0·80	4·5	0·16	2·3

traits are incompatible but increased if desirable traits have favourable genetic correlations. The genetic correlations presented in Table 3 provide information about the expected correlated response in one trait when selecting for another. To bring out the nature and sizes of the correlated responses those expected in six characters following selection for any one of them are shown in Table 6, when for example the best 25% of tested boars are used for breeding. These six characters were chosen as of primary importance by the National Pig Progeny Testing Board.

Favourable responses are negative for food conversion and backfat thickness and positive for the other traits. Apart from that between daily gain and eye muscle area the correlated responses in the above table are favourable. However, they provide only some part of the response obtainable by direct selection for each trait. The compatibility of improvements in speed of growth and food conversion with reduction in backfat thickness and improvement in carcass desirability makes the improvement on these two fronts an apparently straightforward process. From the overall efficiency of pig production their compatibility with a third front, that of reproductive performance, is very relevant but has still to be investigated.

Comparisons of the genetic correlations, used in Table 6 and given extensively in Table 3, with other published estimates are not easy because

of the high sampling error of all estimates. As far as can be judged, there is substantial agreement with the various estimates presented by Johansson and Korkman (1950), Jonsson (1959) and Jonsson and King (1962). There has been no confirmation either here or in the literature of an important antagonism between food conversion and carcass leanness reported by Dickerson (1947) in inbred lines of Poland China pigs. There would appear to be a progressive reduction in the genetic correlation between daily gain and food conversion from about $-0{\cdot}9$, down to $-0{\cdot}6$, as one moves away from the more restricted system of Danish feeding towards complete *ad lib.* feeding.

The results obtained from the principal component analysis have been described in some detail and it only remains to discuss their wider implications. The two analyses carried out on the environmental and genetical components respectively show that in the latter much more of the observed variation in the correlation matrix can be explained by two principal components. This is to be expected as the genetical correlation matrix has excluded many of the attenuating effects produced by errors of measurement. The analysis to this extent makes a closer approach to the underlying relationships but leaves a major problem unsolved. This is to know if, and in what manner, principal components revealed by statistical analysis can be related to biological mechanisms. While it is true that a biological mechanism can give rise to an identifiable component, the reverse is by no means necessarily true. Thus although it is tempting to identify the first principal component with some function of fatness, and advocates of factor analysis would undoubtedly do so, this step may not be justified. Until there are physiological measures of fat metabolism available with which to correlate the fatness factor the identification of factors would be misleading, particularly since they are so dependent on the spectrum of measurements chosen for analysis.

SUMMARY

Estimates of heritabilities and genetic correlations among 35 measurements and scores of British Large White bacon pigs are reported. The data came from pigs tested at the five National Progeny Testing Stations during the period autumn 1957 to spring 1959, and comprised full records on 1936 pigs from 200 sires. Independent analyses were carried out for each sex, and adjustments were made to the data for differences among stations, six-monthly periods and weight at slaughter.

Genetic parameters were estimated from sire components of variation and covariation obtained by conventional heirarchical analyses of variance and covariance. Estimates of the heritabilities and their standard errors are given in Table 2, and of genetic and phenotypic correlations in Table 3. These estimates, which agree in general with other estimates in the literature, indicate that a large part of the variation and covariation is of genetic origin and that carcass traits, growth rate and food conversion efficiency are amenable to change by selection. Moreover, no serious antagonisms were found to exist with regard to improvement by selection.

An attempt has been made to summarise the correlation matrix pattern among 24 of the more important traits by using a principal component analysis. The first two principal components account for a disproportionate fraction of the correlation pattern especially of the genetic correlation

matrix. Two principal components are given for each trait; the first m be associated with measurements of fat depth.

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ESTIMATION OF GENETIC CHANGE IN FARM LIVESTOCK USING FIELD RECORDS

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In the past it has not been possible to measure the genetic changes in performance which have occurred in farm livestock because there has been no means of determining what part of the total change was in fact genetic. Methods using planned comparisons with special breeding groups are now available to measure genetic change in breeding stocks under selection (Gowe, Robertson and Latter, 1959; Goodwin, Dickerson and Lamoureux, 1955; Dickerson, 1960). However, the problem remains in accumulated data or in populations where no control comparisons are to be available. An attempt is to be made in this paper to measure genetic change using field records by comparing the change with time in performance of successive progeny groups of individual sires with the change in the whole population.

The early attempts of Lörtscher (1937) and Nelson (1943) to measure genetic change in herd performance have been criticised because their age correction factors were confounded with year effects and because even small errors in age correction factors derived from other sources could create a serious bias in the estimates of change (Rendel and Robertson, 1950). More recently Elston (1959) presented a scheme for measuring genetic change due to sire selection by measuring the change in the average sire effect with time.

Sources of change in performance

Several factors may contribute to changes in performance with time. There may be changes in nutrition, husbandry and health and there may also be genetic change. In successive performances individuals will change in age. There may be a change in the age distribution of the population and some culling on early performance, the effects of which will be confounded with age differences. Lastly spurious changes such as changes in scale or form of measurement are possible.

A clear plan of the structure of a herd or population and the changes it undergoes with time is given by a three-way classification extending to several time groups (T), age groups (A) and genetic groups (G). Assuming the changes are additive, they can be represented, as in Figure 1, by the small letters which are the deviations from the values of T, A and G respectively in the first square.

This diagram corresponds to that of Rendel and Robertson (1950), and as they have shown, the t's, g's and a's cannot be estimated separately unless one of the deviations is specified. This may be possible if the effect of age changes or time changes are zero or known at any point. Otherwise, one can only deal with differences in rate of change, e.g. $\left(\frac{t_2}{2}-t_1\right)$, but these will tell nothing about the absolute changes.

The partition of change

To partition the total change in performance into its component parts the symmetry of the structure of Figure 1 must be breached in some way. Neither time nor age classes can be exactly repeated for one set of individuals

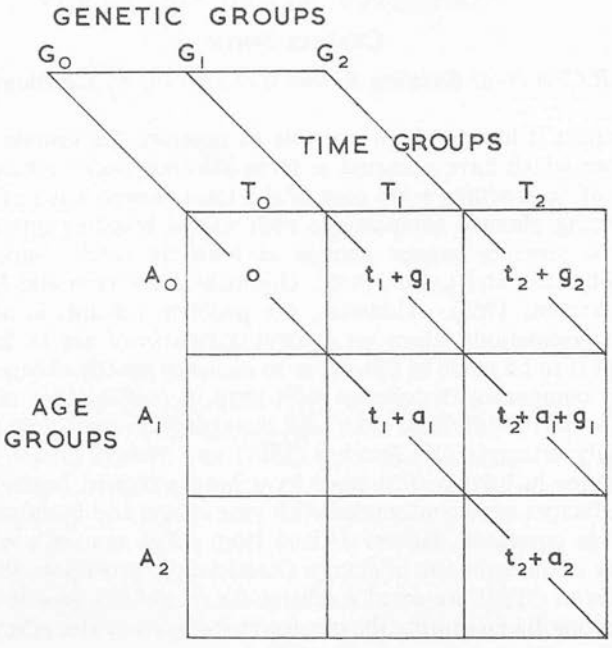

FIG. 1. A diagram of age and genetic changes with time in a herd or population.

but it is possible to produce a new set of individuals having the same average genotype as an earlier set. The random-bred control (Gowe, Robertson and Latter, 1959) and the repeat-mating technique (Goodwin, Dickerson and Lamoureux, 1955, 1960) use this principle, that is:

	T_0	T_1
Control group	0	t_1
Experimental group	0	t_1+g_1

and so the g's and t's and similarly the a's can be estimated. These methods can be used to measure genetic change in stocks at present under selection.

In field data, sires are likely to have progeny born in several years and so they provide some continuity of genotypes by which genetic change can be measured. If the change in performance of a population over one year is represented by $t+g$, then the change in performance of successive groups of progenies of individual sires is $t+\frac{1}{2}g$, assuming their mates are random samples of those available. That is, the genetic change in the population is g, the genetic change in any sire is taken to be zero, so that the genetic change in his progeny over one year is $\frac{1}{2}g$. The difference $(t+g)-(t+\frac{1}{2}g)$ measures half the genetic change in that year. The individual g's and t's

and so also the a's can be estimated in this way. If the changes are linear or alternatively if it is wished to measure their average, they can be accumulated over several years and expressed as a rate of change or total change. Dickerson (1960) has proposed substantially the same principle to measure response to selection in experiments with farm animals, namely the comparison of contemporary progenies by sires of two different generations.

These techniques in fact measure the genetic change due to changes in the array of sires and assume that the same rate of change is occurring in both sexes. Since dams are daughters of sires of the previous generation, it is unlikely that different rates of change could exist in the two sexes over a period of time. The same procedure could be followed using the within-dam change but the effects of dam age and culling may introduce biases. It may be noted that the comparison of each sire with a population average which omits rather than includes that sire's progeny, will lead to some over-estimation of genetic change especially if only a few sires are involved.

Two estimates of change can be used, one derived from the regressions of performance on time, the other from differences in means with time. In a later section of this paper the rate of genetic change in performance has been estimated as $2(b_{PT} - b_{ST})$ where b_{PT} is the linear regression of population performance on time and b_{ST} the pooled within-sire regression of progeny performance on time. To avoid year to year fluctuations in environment, the expression $2b_{(P-S)T}$, twice the pooled within-sire regression on time of the difference between the population and individual sire means, can be used. Using means rather than regressions, the genetic change over y years is given by:

$$\frac{2\,[(\bar{X}_{T_y} - \bar{X}_{S_y}) - (\bar{X}_{T_o} - \bar{X}_{S_o})]}{y}$$

where $\bar{X}_T$ and $\bar{X}_S$ are the population and repeated sire means, or by the average of this expression over the y years (Dickerson, 1960). The regressions will be more efficient estimates of change than the means unless the initial difference $(\bar{X}_{T_o} - \bar{X}_{S_o})$ is taken as zero and known to be without error but this will not be possible in practice. An improved estimate would be obtained by combining the estimates of change derived from the regressions and the means (Leech and Healy, 1959) but this has not been attempted.

Of various non-additive effects which may arise, a sire-year interaction is the most relevant, for it will affect the within-sire change with time. Changes in environment may be either short term fluctuations or long term persistent changes. In the former a sire-year interaction can be regarded as additional error contributing to the variance of the average within-sire change with time and, provided there are many sires, will not bias the estimates of genetic change. If environmental change is of a long term nature, a sire-year interaction will reflect real genetic change in a sire's breeding value and the within-sire change will again be appropriate for estimating genetic change.

Application to field data

The application of the above methods in practice may not be quite straightforward owing to the unbalanced nature of field data. If sires used in several years have been selected on the performance of their early progeny,

there will be some regression to the mean in their subsequent progeny. This will affect the change in performance of progeny of a sire with time and bias the estimate of genetic change. However, if there is a time of decision in selecting or culling sires then the records on progeny born before or after this time can each be used separately to give unbiased estimates of genetic change. Alternatively, the early records can be adjusted to account for the expected regression. In practice, after some initial selection among breeding animals on their progeny records, a progressive type of culling is likely and the bias this causes will be hard to eliminate.

In practice, older sires tend to have older mates. If there are no age effects or effects of culling of dams, the within-sire change provides an estimate of $t+g\frac{(1-x)}{2}$ where x is the regression of age of dam on age of sire. Otherwise the within age class of dam within-sire change in performance measuring $t+\frac{1}{2}g$, will avoid biases arising if the mates of a sire are older progressively culled and from different genetic groups as the sire gets older.

To provide a sound estimate of genetic change over a period of years each year should be well represented. There must be an overlap in time of progenies of different sires for in periods without an overlap, the within-sire change, and so the genetic change, cannot be estimated. The average genetic change per year or the rate of change over a period of years, will usually be required even if the trend is not exactly linear. However, if it be more informative, the genetic change from one year to the next can be estimated although the precision of the individual estimates will be less.

Variance of estimates

Some indication of the reliability of the estimates of genetic change is needed and approximate standard errors can be obtained. The maximum variance of $2(b_{PT}-b_{ST})$ may be written $4(Vb_{PT}+Vb_{ST})$ assuming the regressions to be positively correlated as is likely but not necessary. If the estimate $2b_{(P-S)T}$ is used, the variance is simply $4Vb_{(P-S)T}$.

The theoretical variance of $2(b_{PT}-b_{ST})$ may be written approximately

$$4\sigma^2\left(\frac{1}{NT_Y}+\frac{1}{\Sigma n_s T_y}\right) \qquad \text{.....(1)}$$

where σ is the standard deviation of the trait concerned, N is the total number of records per year and n_s the number of records per year for the sth sire, Y the total number of years and y the number of years in which the sth sire is present and $T_Y=\frac{Y(Y^2-1)}{12}$ and $T_y=\frac{y(y^2-1)}{12}$. Since the first term in expression (1) will be much smaller than the second unless many sires are spread over the whole period, the variance reduces approximately to

$$\frac{4\sigma^2}{\bar{n}\underset{s}{\Sigma}T_y} \qquad \text{.....(2)}$$

where $\bar{n}$ is the average number of records for each sire in any year. An approximate variance of the estimate $2b_{(P-S).T}$ is also given by this expression. It should be noted that this variance does not take into account the degree of overlap of different sires over time.

The standard error of an estimate of genetic change derived by this method from a given body of data can be obtained from expression (2) and will indicate whether an analysis of this type will be worthwhile. For example if 10 sires had an average of 20 progeny per year, six sires in each of three years and four sires over five years, then $\bar{n} = 20$, $\Sigma T_y = 6\times2+4\times10 = 52$ and the standard error of an estimate of genetic change would be about $2\sigma/\sqrt{20\times52} = \cdot06\sigma$

Planned use of repeated sires

In planning to repeat sires over several years specifically to measure genetic change, expression (2) can be used as a guide to design. If s sires are used over y years with $\bar{n}$ progeny each per year the variance of the estimate of genetic change is proportional to the inverse of T_y and to the inverse of $\bar{n}s$. Since T_y increases approximately as y^3, extending the number of years over which individual sires have progeny will be more effective in reducing the variance than will increasing the total progeny of repeated sires in each year. To avoid a possible bias from a sire-year interaction many sires, rather than few, should be repeated. The actual requirements, in terms of number of years and number of progeny from repeated sires, to measure a certain rate of change can be determined. To demonstrate as significant a rate of change of say g standard deviation units per year a standard error of estimate of $\frac{1}{2}g\sigma$ would be required. Equating this to expression (2) then:

$$\bar{n}sT_y \simeq \frac{16}{g^2}$$

To economise on facilities, the breeding life of repeated sires should be as long as possible, though it will take correspondingly as many years to show any genetic change. The total number of progeny per year from repeated sires is proportional to the inverse of the square of g. Thus it takes four times as many records to measure with the same accuracy a genetic change of $0{\cdot}1\sigma$ as one of $0{\cdot}2\sigma$, 25 times as many as one of $0{\cdot}5\sigma$ and 100 times as many as one of $1{\cdot}0\sigma$. Very large facilities will be required to demonstrate a small rate of change.

By increasing the number of progeny from repeated sires in their first and final years, and omitting progeny during intermediate years, the same precision can be obtained with fewer total progeny per sire. The variance of an estimate of genetic change obtained in this way (B) is approximately $8\sigma^2/N_1(y-1)^2$ compared with $4\sigma^2/\bar{n}s\,T_y$, the variance of the previous estimate (A), where N_1 and $\bar{n}s$ are the total number of progeny of repeated sires in each year in their respective systems. The rate of genetic change in a population can also be measured by using a random-bred control group (C), (Gowe, Robertson and Latter, 1959). The regression of the difference of the population mean and the control groups mean on time measures the rate of genetic change with a variance σ^2/N_cT_y where N_c is the number of progeny per year in the control group.

The total number of progeny required by the three methods (for A, $y\bar{n}s$; B, $2N_1$; C, yN_c) to obtain the same precision for an estimate of genetic change over a number of years can be compared. The ratios of the required

numbers of progeny in B and in C to that in A are given below for perio up to 10 years.

	Years									
	1	2	3	4	5	6	7	8	9	10
$\frac{B}{A}$	—	1	0·67	0·56	0·50	0·47	0·44	0·43	0·42	0·41
$\frac{C}{A}$	—	0·25	0·25	0·25	0·25	0·25	0·25	0·25	0·25	0·25

A saving of over 50% of total progeny is made by testing sires extensive initially and again after a 5–10 year period. A scheme of this type is pa ticularly well suited to artificial insemination and storage of semen ov many years. The facilities required by the random bred control method a only one quarter of those needed by the repeated sires method as show above. Moreover, the term T_y is not limited by the breeding life of sire as in the previous cases. Unless possible biases are considered importa (Goodwin, Dickerson and Lamoureux, 1960) the random bred contr method must be the method of choice to measure genetic change in population under selection.

AN APPLICATION

Material

The data used to demonstrate the application of this method to measu genetic change were records kept by a pedigree pig breeder over the yea 1950–58 on some 1,188 Large White litters. Over this period there we striking changes in several carcass traits, as shown in Table 1.

TABLE 1

Herd averages in six carcass traits from 1950–58

Year	Number of litters	Age at slaughter (days)	Carcass weight (lb.)	Dressing out (%)	Carcass length (mm.)	Fat depth shoulder (mm.)	Fat dept mid-back (mm.)
1950	72	230	165	75·7	785	50·9	27·9
1951	41	224	158	75·4	784	50·6	28·0
1952	115	228	158	75·3	790	52·5	27·1
1953	136	226	153	73·9	798	49·9	24·8
1954	148	215	151	73·9	797	48·0	24·6
1955	146	213	151	73·9	804	49·5	24·0
1956	172	199	150	74·1	811	49·3	23·8
1957	177	204	148	73·6	814	47·3	22·3
1958	191	197	150	73·9	824	47·4	21·8
Total change		−33	−15	−1·8	39	−3·5	−6·1
Estimated within year standard deviation		22·4	5·6	2·1	23·6	5·0	3·9

The total changes in age at slaughter, carcass weight, carcass length an mid-back fat depth were greater than their respective estimated within ye

standard deviations. The change in carcass weight may account for some part of the changes in backfat thickness, dressing out % and age at slaughter. Carcass length on the other hand increased by 39 mm. in spite of the decrease in carcass weight. The trends were fairly linear over the period, so that the average change per year is a meaningful figure. Gross changes, due for example to changes in husbandry or changes in measurement, will show up sharply in the year means, for example the decrease of 5 lb. in carcass weight from 1952 to 1953, coinciding with decreases of 1·4%, 2·6 mm. and 2·3 mm. in dressing-out %, shoulder and mid-back fat depth respectively.

The pedigree and the litter averages for the above six carcass traits were available for each litter. Only pigs which were slaughtered for bacon at 190–240 lb. live-weight, an average of 5·5 per litter, had carcass records. The remainder, about 1·2 per litter, were either retained for breeding or sold for pork at lighter weights. The measurements were taken co-operatively by the factory staff and the farmer and some attempt was made to standardise them over the years.

In contrast to the changes from one year to the next, seasonal differences in performance were negligible. Selection among sows seemed to depend on their own reproductive performance rather than on the carcass measurements of their litters. Thus sows that were culled, weaned about 3 pigs less than average in their last litter but their pigs were average in their carcass traits. Of the 85 boars having progeny, 21 each had over 20 litters spread over two or more years and their 998 litters were used to estimate the within-sire change with time. Selection among sires was measured by comparing the progeny from each of these 21 sires in their first year of use with the progeny of contemporary young boars which were not retained for breeding. The average selection differentials were −0·82 days for age at slaughter, −0·09 lbs. and −0·16% for carcass weight and dressing-out % respectively, +5·09 mm. for carcass length and −1·33 mm. and −1·63 mm. for mid-back and shoulder backfat thickness respectively. Those for backfat thickness and carcass length are thus about one third of a standard deviation and the others much less. This amount of selection for backfat thickness and carcass length among young boars is likely to bias the estimates of genetic change in these traits.

Measurement of genetic change

A visual representation of this method of estimating genetic change may be more convincing if less precise than a statistical one. Herd and individual sire progeny averages in each year are shown graphically for carcass length in Figure 2 and demonstrate the nature of the differences on which the method depends.

Year to year changes in sire progeny means were usually less than the annual changes in the herd average, so that relative to the herd average individual sire progeny means fell with time. This is convincing evidence that genetic change in carcass length was taking place.

The average annual change in the herd, as estimated by the linear regression of each trait on time, measures $t+0{\cdot}98g$, the average age of sows in the herd increasing by half a month per year. The pooled within age class of sow within-sire regression measures $t+\frac{1}{2}g$. Because of an increase of six months in the average age of dams per year increase in age of sire, the ordinary

pooled within-sire regression measures $t+\frac{1}{4}g$ if there are no effects of cull or age differences among dams. The estimates of genetic change deri from these regressions are given in Table 2.

The individual within-sire regressions showed heterogeneity, but due contemporary sires having different regressions, perhaps from sire-y interactions, rather than to the regressions over one period being differ in sign or magnitude from those in another. The pooled within-sire regr sions differed significantly, trait by trait, from the total regressions.

Selection among sires may bias the estimates of genetic change. In attempt to reduce this bias the analyses were repeated after omitting

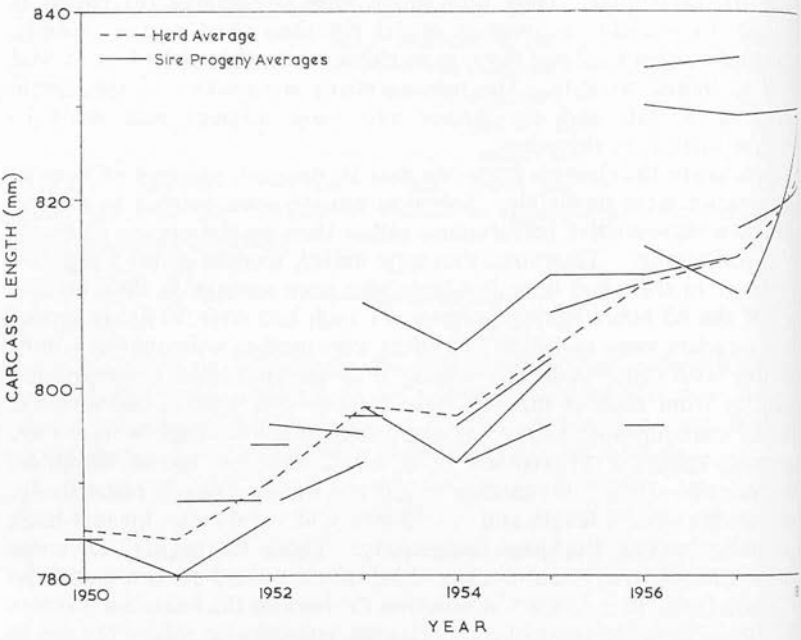

FIG. 2. Graph of herd and individual sire progeny averages for carcass length in each y

first 15 litters of each sire, since it appeared that sires were selected on th first 10–15 litters, for boars used after siring 15 litters continued to be u for some time. One sire produced 200 of the 998 litters over a period $5\frac{1}{2}$ years. Since the pooled within-sire regressions depend disproportiona on the changes within this sire's progeny the estimates of genetic change h been recalculated after omitting the data on this sire, and these are a shown in Table 2.

The change in progeny from repeated matings will provide an estim of environmental change, but this will be biased if the parents have b selected or if the dam's age affects her litter's performance. In these d there were 179 repeated matings, some appearing several times and different intervals. These were combined to provide an estimate of the av age environmental change per year. The genetic change is taken as t difference between this and the total change and is shown in Table 2.

By and large, the estimates of genetic change calculated by differ methods give rather similar results. Those from the within-sire regressi

TABLE 2

Estimates of the annual genetic change (with approximate standard errors)

	Age at slaughter (days)	Carcass weight (lb.)	Dressing out (%)	Carcass length (mm.)	Fat depth shoulder (mm.)	Fat depth mid-back (mm.)
Average annual change	$-4{\cdot}86\pm0{\cdot}18$	$-1{\cdot}56\pm0{\cdot}06$	$-0{\cdot}18\pm0{\cdot}02$	$4{\cdot}99\pm0{\cdot}22$	$-0{\cdot}53\pm0{\cdot}05$	$-0{\cdot}74\pm0{\cdot}04$
Annual genetic change estimated from:						
(1) Within age class of sow within-sire	$-0{\cdot}76\pm1{\cdot}50$	$-1{\cdot}45\pm0{\cdot}37$	$-0{\cdot}36\pm0{\cdot}14$	$6{\cdot}36\pm1{\cdot}50$	$-1{\cdot}14\pm0{\cdot}33$	$-0{\cdot}52\pm0{\cdot}24$
(2) Within-sire	$-0{\cdot}11\pm0{\cdot}81$	$-0{\cdot}74\pm0{\cdot}21$	$-0{\cdot}25\pm0{\cdot}08$	$5{\cdot}26\pm0{\cdot}79$	$-0{\cdot}89\pm0{\cdot}18$	$-0{\cdot}63\pm0{\cdot}14$
(3) Within-sire omitting the first 15 litters per sire	$+0{\cdot}69\pm1{\cdot}07$	$-0{\cdot}75\pm0{\cdot}27$	$-0{\cdot}26\pm0{\cdot}10$	$5{\cdot}49\pm1{\cdot}08$	$-1{\cdot}03\pm0{\cdot}22$	$-0{\cdot}63\pm0{\cdot}17$
(4) Within-sire, omitting one sire	$-3{\cdot}72\pm1{\cdot}20$	$-0{\cdot}09\pm0{\cdot}30$	$-0{\cdot}10\pm0{\cdot}12$	$5{\cdot}96\pm1{\cdot}19$	$-1{\cdot}13\pm0{\cdot}25$	$-0{\cdot}86\pm0{\cdot}21$
(5) Repeated matings	$+0{\cdot}66\pm2{\cdot}16$	$-1{\cdot}36\pm0{\cdot}58$	$-0{\cdot}45\pm0{\cdot}17$	$4{\cdot}93\pm1{\cdot}40$	$-1{\cdot}09\pm0{\cdot}40$	$-1{\cdot}06\pm0{\cdot}31$

and repeated matings are similar to the estimates from the within ag dam within-sire regressions indicating that the effects of age and selec among sows were not serious sources of bias. Omitting the first 15 li per sire from the analyses had little effect on the estimates. Perhaps s selection on 15 litters was quite accurate, regression to the mean in l litters was small. On the other hand, the estimates may agree because greater weight is thrown on the change within the sire with 200 lit Omitting the sire with 200 litters from the analyses results in different mates of genetic change in two traits, age at slaughter and carcass wei but not in the other four. This provides additional confidence in the estim of genetic change for carcass length and backfat thickness but less confid in the estimates for other characters.

There appears to have been little genetic change in age at slaug although there was an observed decrease of 4·9 days per year. Ge changes in the other five traits, however, were all significant. Carcass we seems to have decreased both genetically and environmentally while genetic change in dressing out % was apparently larger than the total cha Genetic changes in these two traits are not necessarily spurious for t heritabilities are about 0·3 (e.g. King, 1957). Further, the estimated ge changes are compatible, a 0·3% decrease in dressing out % correspon to a 0·6 lb. decrease in carcass weight.

The genetic changes for carcass length and backfat thickness ca viewed with more confidence, all estimates being significant and in g agreement with one another. The genetic change in carcass length wa fact greater than the total change. This is quite possible, for the decrea carcass weight would bring some decrease in carcass length, while observed change was in the opposite direction. The genetic change backfat thickness equalled or exceeded the total changes. Here the decr in age at slaughter should bring an increase in backfat thickness and decrease in carcass weight will tend to reduce backfat thickness.

How were the genetic changes brought about? The breeder pursu policy of purchasing boars from other pedigree breeders and 80% of litters were sired by purchased boars. Within the herd he culled sows poor litter performance and selected gilts for breeding from sows with g litter records. Genetic improvement in carcass traits could have come f buying young boars from improved herds and from selection among yo boars on their progeny performance. The progeny of young boars ente the herd each year were about 3 mm. longer than the average of the h but there was no consistent superiority for other traits. Either the wi population of Large White pedigree herds was changing at much the sa rate as this particular herd, or, as is more probable, the breeder grew m and more selective in the herds he bought from. The amount of selec practised among the young boars coming into the herd in any year has b noted earlier. This system of progeny testing and selecting young bo must have played a large part in producing the genetic changes in the h

Age effects of dams

Once the genetic change is known the effect of age of dam on litter's performance can be calculated. Pigs have a farrowing interva about six months so that the differences in any one year between prog

of second, third, fourth, etc. litter sows and of gilts measure respectively $\left(a_1-\frac{g}{4}\right), \left(a_2-\frac{g}{2}\right), \left(a_3-\frac{3g}{4}\right)$ etc. where g is the annual genetic change and the a's the age effects of the dams. These quantities were estimated by a least squares within-sire within year analysis among litters up to the fifth, there being more than 100 litters in each group. To solve for the a's the estimate of g used was that derived from the within age group of dam within-sire regression. These estimates of the effect of dam's age, or parity, are shown for each trait in Table 3. They are not uncorrelated because a common estimate of genetic change was used for their determination, and because they all depend on differences from the average performance of gilt litters. They are, of course, confounded with any culling of dams which has taken place.

TABLE 3

Effects of dam's age, estimated as deviations from the performance of gilt litters

	Age at slaughter (days)	Carcass weight (lb.)	Dressing out (%)	Carcass length (mm.)	Fat depth shoulder (mm.)	Fat depth mid-back (mm.)
Second litter sows	−6·6	−0·34	0·04	2·80	−0·21	0·28
Third „ „	−7·1	−0·06	0·16	3·54	0·08	0·46
Fourth „ „	−8·5	−0·84	−0·10	0·85	−0·45	0·41
Fifth „ „	−7·7	−0·98	−0·16	2·90	−0·27	0·38
Average standard error	2·34	0·59	0·22	2·45	0·53	0·40

The effect of dam's age on the performance of her litter was only significant for age at slaughter. Pigs from gilt litters were about 6–8 days older at slaughter than other pigs, and this may have been largely due to their average weaning weight being 1·8 lbs. less than for pigs from older sows.

Before allowing for genetic differences between age groups of sows, pigs from older sows had about 0·4 lb. more carcass and about 0·2% higher average dressing-out % than pigs from gilt litters. When the genetic differences between age groups of dams were taken into account, these deviations were reversed in sign but none of them were significant. The position was the same for carcass length and backfat thickness. Within any year the older sows produced pigs which were shorter on average by 1·4 mm. and fatter on average by 0·6 mm. than pigs from gilts but when genetic differences between groups were allowed for these trends were reduced or reversed, though again none of the age effects was significant.

DISCUSSION

Dickerson (1960) has discussed the merits of various techniques which can be used to measure genetic changes in experimental populations. As yet there has been little application of these methods to farm livestock. The method of Elston (1959) and that given here, both depending on changes in the array of sires with time, are the first to provide some means of measuring genetic changes in performance of farm animals using field records. Though having the advantage over conventional methods in that

they require no additional facilities, two factors may prevent the gene use of these methods in practice. There may not be sufficient sires ea spread over a sufficient period of time to demonstrate the small rates genetic change, say less than one tenth of the standard deviation in a tr per year, likely in livestock populations. If there are, there is still likely be some initial selection and progressive culling among sires which w throw doubt on the estimates of change. If these two points are not releva then the methods are worthy of consideration to measure past and curr genetic changes. The same principle can be applied more efficiently planning to use randomly chosen sires over a long period of time, as propo by Dickerson (1960), rather than relying on sires occurring in practi However, in terms of the total number of progeny required, the random-b control group is a more efficient means of measuring genetic change.

Animal geneticists have been ready to support national livestock impro ment schemes, without any efficient means of assessing their worth in practi With the development of methods of measuring genetic change, this n no longer be the case and a critical evaluation of each scheme is now possib It is for the geneticist to inform the authorities of this development and urge the adoption of some method to measure the effectiveness of all curr and proposed improvement schemes. Then if progress falls far bel expectation a critical appraisal can be made and remedial action taken. Britain, for example, the amount of genetic improvement accruing from recording and pig progeny testing is the basic question relevant to th schemes, yet up to now no assessment has been possible.

While emphasis in this paper has been with measuring genetic chan the effects of general environmental changes are measured at the same ti It may even be possible to allocate the environmental change to vari sources such as food consumed, yearly and seasonal changes, health housing and so on (e.g. McDaniel, Plowman and Davies, 1961).

SUMMARY

This paper describes the estimation of genetic changes in farm livest using field data. The method proposed depends on a difference in rat change in performance of the population and of the successive proge of individual sires. The change in the population with time is taken $t+g$, where t represents environmental change and g represents gen change, while the within-sire change is taken as $t+\frac{1}{2}g$. Their differe measures half the genetic change.

This principle can be applied, with certain precautions, to field data wh there is some spread of sires over time. The method has two advanta over other methods in that past as well as current changes can be measu and no additional facilities are required. However, selection among s may bias the estimates of genetic change. Approximate sampling error the estimates of change can be obtained and hence the rate of genetic cha which a certain body of data will demonstrate to be significant can estimated.

The method was applied to a set of pig records collected over nine ye by a private pig breeder. There was considerable change with time in six traits examined and in at least three of them there appeared to have b a substantial genetic change accounting for the whole of the observed cha

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A recent paper (Van Vleck and Henderson, 1961. *J. Dairy Sci.*, **44**: 1705), uses a variation of the same principle given here to measure genetic trend in dairy cattle performance.

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GENETIC CHANGE OF BACKFAT THICKNESS IN THE DANISH LANDRACE BREED OF PIGS FROM 1952 TO 1960

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OVER the past sixty years the Danish Landrace breed has improved steadily in carcass quality and other characteristics (Clausen and Nørtoft Thomsen, 1962). This improvement is commonly attributed to progeny testing and the system of testing has been widely acclaimed and imitated, especially in Europe. Generally, most of the observed change in performance has been assumed to be genetic in origin, though this has never been established. Now that methods have been developed to measure genetic change in field records (e.g. Smith, 1962) it was thought worthwhile to examine the nature of the improvement in the Danish Landrace and to ascertain if the popular acceptance of genetic improvement is justified.

This paper describes an attempt to measure the genetic change in backfat thickness in the Danish Landrace breed from 1952 to 1960. During this period backfat thickness decreased by more than two standard deviation units and there were also major favourable changes in other economically important traits.

MATERIAL AND METHODS

The Danish system of progeny testing and the organisation of State-recognised breeding centres have been described on several occasions (e.g. Lush, 1936; Jonsson, 1958). Litter groups of 2 hogs and 2 gilts, chosen by the breeder, are tested with individual feeding. A sire or dam may have one or many litter groups tested but the test results are published for each litter group. Each breeding centre is obliged to test one litter group per year for every two approved sows in the herd. The breeding centres tend to be small, having on average about 10 sows and 2–3 boars. At the three progeny testing stations the feeding and housing of the pigs are closely standardised to keep conditions as uniform as possible among the stations over the years.

The data for the analyses which follow were abstracted from the annual reports of the Danish progeny testing stations for the years 1952–60 (Clausen and Nørtoft Thomsen, 1954–62). These reports provide litter averages for backfat thickness and other traits, classified under station, breeding centre, sire and dam as shown below in an extract from the 1959–60 report.

The date of birth of the sire and the dam are given along with the farrowing date of the litter group tested. It is thus possible to classify the data by age of either parent or by year of birth of parent and to abstract litters by the same sire or dam in different years.

The method used to measure genetic change is a variation of that described by Smith (1962). It depends on the change in performance from one year to the next of progeny groups from particular sires and from particular

dams. If the performance of the progeny is expressed as a deviation from the year mean any environmental difference between years is removed. It is assumed that the genetic merit of a parent does not change over time but the average genetic merit of its mates will change as the population changes in genetic merit. The difference in performance in two years of progeny from a particular parent will therefore be half the genetic change in the population.

Though this principle to measure genetic change is simple, its application to a set of data will often be difficult and require modification. More or less than half the genetic change may be involved if a parent's mates are not random samples of those available in each year. Assuming the non-random allocation of mates is due only to the association of age of mate with age of parent, the portion of the genetic change involved can be determined from consideration of the difference between the average age of the mates in the two years. A more serious problem may arise if there has been selection among parents based on the records of their progeny in the first year,

Extract from the report for 1959 *to* 1960 (*Station Fyn*)

Breeding centre (farm)	Farrowing date of litter	Sire: Number and name	Sire: Date of birth	Dam: Number	Dam: Date of birth	Backfat thickness (cm.) of litter group
Aalsbogaard	10. 3.59	No. 95, Pioneer	31.12.57	No. 78	7.6.57	2·9
,,	26.11.59	No. 75, Merkur (6891) †	—	No. 79	16.5.58	3·1
,,	26.11.59	No. 100, Odbo	28. 2.58	No. 83	16.5.58	2·6
,,	17.12.59	No. 100, Odbo	28. 2.58	No. 84	16.5.58	3·0

† Herd book number.

so that only the better parents are retained and have progeny in a second year. In this case, even if there was no genetic change in the population there would be some regression to the mean in their subsequent progeny performance. The difference between the progeny in the first and second years would lead therefore to biassed estimates of the genetic change. Adjustment of the first records by the theoretical expected regression of second record on first record will remove the effects of selections among parents, and the estimates of genetic change will be unbiassed. The difference in the progeny of particular dams in two or more years will include effects of maternal age on progeny performance. The effects of maternal age on the backfat thickness of progeny are believed to be small and have been ignored in the analyses.

The initial sections of the results present some comparisons of progeny from groups of parents, classified by age and by year of birth. These serve as a preliminary guide to the nature of the observed change in performance and lead to a closer study of the extent of selections among parents as an indication of the rate of genetic change.

RESULTS

Total change in performance

The change in performance of Landrace pigs tested at the Danish progeny testing stations from 1952–60 is shown in Table 1.

During this period backfat thickness decreased by 5·7 mm. or more than two standard deviation units. The changes in daily gain, food conversion and carcass length were also large and favourable. The trend in backfat thickness from 1952–60 was quite linear, the average annual change being —0·71 mm. Performance at the three testing stations changed concurrently over the period and changes in rank among the stations were consistent over several years.

Birth-year groups of parents

The change in performance of successive yearly progeny groups of sires and of dams born in a particular year has different components from the observed change in the whole population. Both will include environmental

TABLE 1

Performance of Danish Landrace pigs from 1952 *to* 1960

Season	Backfat thickness (mm.)	Daily gain (g. per day)	Food conversion (feed units per kg. gain)	Carcass length (cm.)
1952–53	34·2	665	3·06	93·4
1953–54	33·3	675	3·03	93·7
1954–55	32·6	678	3·03	93·8
1955–56	32·1	680	3·01	94·1
1956–57	31·2	681	2·97	94·4
1957–58	30·5	685	2·95	94·8
1958–59	29·7	685	2·96	95·1
1959–60	28·9	684	2·95	95·6
1960–61	28·5	696	2·91	95·7
Total change 1952–60	−5·7	+31	−0·15	2·3
Within sex standard deviation (1954-61) †	2·7	30	0·13	1·9

† Jonsson (1961).

change, but the former will include effects of selections among parents and only a portion of the genetic change. Here the portion will be less than a half because the average age of mates increased with age of parent. The regression of age of mate on age of parent was about 0·2, so in fact only 0·4 of the genetic change will be involved. To study the sums of these components all progeny groups at each station in each year were classified separately by year of birth of sire and of dam. The differences between the successive yearly sets of progeny for each birth class of parent are summarised for sires and for dams in Table 2. They represent the sum of the environmental change, the effects of selection among parents in the previous year and about 0·4 of the annual genetic change.

The successive yearly progenies of parents born in a particular year had markedly different performances. The average change in their progeny from one year to the next was almost as large as the observed change in the population. Thus all age groups in the population were improving concurrently and at much the same rate. This suggests that environmental change was predominant but it is also possible that intense selection among parents coupled with genetic change in their mates could account for these changes in performance.

Parents of different ages

By comparing the contemporary progeny of parents of different environmental differences disappear while genetic differences remain. a genetic decrease in backfat thickness in the breed, progeny from parents should have less fat than progeny from old parents tested in same year. In this case, because older parents tend to have older a larger portion, about 0·6, of the genetic difference between pare

TABLE 2

Differences in performance between successive yearly progenies of gro of sires and of dams classified by year of birth

Progeny performance	Backfat thickness (mm.) Progeny of sires	Progeny of dams
2nd year *v.* 1st year	−0·72±0·16	−0·61±0·12
3rd year *v.* 2nd year	−0·60±0·09	−0·47±0·07
4th year *v.* 3rd year	−0·46±0·16	−0·46±0·10
later years *v.* 4th year	−0·88±0·25	−0·87±0·17

involved. In addition to genetic differences between the age groups, will be differences caused by the selection of the better parents in each These will tend to improve the relative position of progeny from the parents. For this analysis, progeny groups were classified independ by age of sire and age of dam for each station in each year and the av backfat thickness of each class was expressed relative to the statio mean. The results are summarised for the eight years and three st in Table 3.

TABLE 3

The performance of contemporary progeny from parents of different ag relative to their station average

Age of parent	Backfat thickness (mm.) Progeny of sires	Progeny of dams
1 year	−0·07±0·13	−0·09±0·12
1–2 years	−0·03±0·03	−0·01±0·03
2–3 years	0·03±0·05	0·08±0·06
3–4 years	0·22±0·14	0·19±0·08
Over 4 years	−0·16±0·10	0·04±0·15

The progeny of old sires and of old dams were only slightly fatter the contemporary progeny of young sires and young dams. This ind that the portion 0·6 of the genetic change was almost cancelled by the e of selection among parents after each testing. Hence if the extent o selection can be measured it may provide some indication of the g change. Conversely, if all the observed change were genetic change a r intense degree of selection among parents in each year could be expect

Selection among parents

The critical part of these comparisons has been the extent of sele for low backfat thickness among parents in each year. The degre

selection practised can be evaluated by measuring the superiority in the first year of progeny from parents having progeny groups tested in two or more years. The average performance in the first year of progeny from such parents was found separately for sires and dams at each station and the results are presented in the second column of Table 4. These figures are only part of the full abstraction of the data which will be described in detail in the next section.

Sires with progeny appearing in two or more years were selected to some extent for low backfat thickness on the basis of their progeny records in the first year. However the reverse was the case for dams, those with fatter

TABLE 4

The performance, relative to the station year mean, of the progeny from parents with progeny groups tested in consecutive years

Station	No. of parents	Backfat thickness (mm.) (progeny averages) 1st year	2nd year	Average period (months) between records (*m*)	Average changes in age (months) of mates (*n*)
Progeny of sires					
Sjaelland	155	−0·56	0·00	11·1	2·9
Fyn	177	−0·57	−0·19	11·4	2·8
Jylland	167	−0·02	+0·04	11·1	4·7
All stations	499	−0·38	−0·05	11·2	3·5
Progeny of dams					
Sjaelland	189	0·63	0·18	11·6	3·7
Fyn	151	0·59	0·38	11·2	0·1
Jylland	168	0·67	0·12	11·6	2·2
All stations	508	0·63	0·21	11·5	2·2

than average progeny in the first year going on to have further groups tested. In neither case was selection intense, the average selection differentials being each about one-third of the standard error of the parent's progeny average. The parents represented in Table 4, however, accounted for only about 30% of the sires and 20% of the dams in their particular age group or birth class at subsequent testing. The remainder of the parents in each group were being tested at the testing stations for the first time. This small proportion, and the mildness of the selection among parents, may explain why the different directions of the selection among sires and among dams has not made itself felt in Tables 2 and 3, that is, at the same age sires and dams had equivalent progeny and the changes in successive progenies of parents classified by year of birth were similar for sires and dams. Moreover, it was found that there was no essential difference between the contemporary progeny of parents being tested for the first time and those of parents which had been tested previously. It was concluded that selection among parents in each year, tested and untested, was mild and could have had only small effects on differences between contemporary progenies from parents of different ages or between the successive yearly progenies of parents born in a particular year. Consequently, following the arguments in the previous

sections, it is also concluded that the extent of the genetic change in bac thickness must also have been small.

Estimation of genetic change

The principle, and the modifications, of the method proposed to esti genetic change have been described already. The data required for analysis were records in two or more years of progeny from partic parents, and these were abstracted from the annual reports. Several res tions were imposed in abstracting the data to avoid possible effects w might bias the estimates of genetic change. First, to avoid dealing with parents which might have been selected on previous records, only pa under three years of age at the birth of their first set of tested progeny included. About four-fifths of the sires and two-thirds of the dams extr were in fact under two years of age then. Many parents had progeny te in three, four and even five years but the data were restricted to the and second sets of records which had to be in consecutive years. continuous sequential selection among parents on intermediate reco thus avoided. Though the period between records was then rather s around 12 months, it was still possible to estimate the genetic change some accuracy because of the large number of parents involved. A fu restriction excluded sires having less than 8 months between their pro groups in the first and second year, so that the average period betwee two sets of progeny was around 12 months.

Records on the progeny of sires and of dams tested in two consec years by the same breeding centre (farm) at the same station were abstr from the annual reports but with the above restrictions. The record cluded year of birth of parent, mate and litter, the period between groups in the two years and the number of litter groups per sire in each The backfat thickness of each litter, relative to the station-year mean also recorded. The results are summarised and presented in Table 4.

There was selection among parents on the records of their proge the first year, though in opposite direction for sires and dams. Ev there was no genetic change in the population there would be some regre to the mean in their subsequent progeny performance. In fact there a regression to the mean by the second set of progeny. But was the regre only that expected following selection on the initial records or was ge change also involved through a changing population of mates? The e of the regression on initial records can be calculated theoretically knowledge of the heritability of backfat thickness and the number of pr tested per parent in the first year. The difference between the regr performance in the first year and the observed performance in the se year will provide an estimate of the genetic change.

The heritability of backfat thickness in the Danish Landrace is 0·5 (Fredeen and Jonsson, 1957; Jonsson and King, 1962). The theore regressions of subsequent performance on initial records are then 0·44, 0·54 and 0·61 for parents with respectively 1, 2, 3 and 4 litter g of four pigs tested in the first year. The deviations from average ba thickness in the first year ($\bar{X}_1$), (Table 4, column 2) were regressed t mean by these regression factors ($b_{2.1}$) and compared with the obs deviation in the second year ($\bar{X}_2$) (Table 4, column 3). The annual ge

change in backfat thickness was then estimated from the data on sires and dams at each station by the expression:

$$2(b_{2\cdot1}\,\bar{X}_1-\bar{X}_2).\ \frac{12}{m}\ \frac{12}{12+n}$$

and the results appear in Table 5. The quantities m and n are given in columns 4 and 5 of Table 4. The factors $12/m$ and $12/(12+n)$ respectively adjust for the average period between progeny records in the two years being m months and for the age of mates in the two years having increased by n months.

The six estimates of genetic change have rather large sampling errors but in general indicate that there has been some genetic reduction of backfat thickness in the Danish Landrace from 1952 to 1960. However, it appears

TABLE 5

Estimates of annual genetic change in backfat thickness from 1952 *to* 1960

Station	Annual genetic change in backfat thickness (mm.) Calculated from sire progenies	Calculated from dam progenies
Sjaelland	−0·33±0·21	0·00±0·27
Fyn	−0·05±0·21	−0·45±0·27
Jylland	−0·17±0·21	0·12±0·27
All stations	−0·18±0·12	−0·11±0·16

Overall combined estimate −0·15±0·10

that not all of the observed change in performance was genetic change. The overall combined estimate of genetic change was −0·15±0·10 mm. per year and this represents only about one-fifth of the observed change of −0·71 mm. per year.

A supplementary estimate of the genetic change in backfat thickness was obtained from the progeny of 56 repeated matings, all that were found in the annual reports from 1952–60. The average backfat thickness of the first set of progeny of these repeated matings was 0·08 mm. and that of the second set of progeny was 0·18 mm., expressing performance as a deviation from the station-year mean. The average record of the first set of progeny was adjusted as before by the theoretical regression of second record on first record. Here the regression coefficient was 0·53 since the litter groups in the two years were from full-sib litters. The annual genetic change was estimated as −0·18±0·35 mm. by the expression given above, with m the period between the litter groups and n the increase in the age of mates both being 10 months. With a standard error of this magnitude the agreement with the previous estimates may be quite fortuitous.

DISCUSSION

Though the principle of measuring genetic change in field records is straightforward, its application may be beset with uncertainties which can

never be completely resolved. Consequently the estimates are always lik to contain some element of doubt. For this reason the techniques used h should be regarded as salvage methods to recoup some information genetic change from data where none would otherwise be available. Th are not presented as the solution to the problem of measuring genetic cha in all current and proposed breeding schemes. Better methods are availa for measuring genetic change, for example by using randomly bred con stocks or repeat mating plans. The onus is on those authorities concer with livestock improvement schemes to include some such provision measuring genetic change. Then the effectiveness of each scheme co be measured as it progresses. Yet most national breeding schemes l such a provision and apparently this deficiency is not even recognised. T common practice of assuming that the observed change is genetic chang quite invalid in principle and is also likely to be invalid in practice.

The uncertainties involved here in measuring genetic change are lik to arise also in other sets of data on farm livestock. They involve the breed aims and policies, their expertise, their familiarity with their stock, the c tinuous culling of animals for many reasons, the overlapping of generati maternal effects on performance and so on. Most of the effects wil difficult to assess and even considered adjustments may be inappropri The aims and standards of the individual breeder are likely to change o the years, as may his breeding policy. Some breeders may employ co pensatory matings to improve their stocks while others may use assorta matings, as judged by earlier records, in their efforts to have their st perform to advantage at the testing stations. In either case the differe in a parent's progeny performance, and so also the estimates of gen change, would be affected by non-random groups of mates used. In th selections breeders may use additional information by way of appeara or pedigree, sib or progeny records, made either on the farm or at the test stations. Selection may therefore be more accurate than would be suppo from the number of progeny tested, so that the theoretical regressions u would tend to overadjust the first set of records. Selections partially ba on correlated traits may have the same effect. However, the actual regr sions of second record on first calculated from the data were, in view of th standard errors, in reasonable agreement with the theoretical estimates. is interesting to note that if no adjustment of the initial records had be made, the estimates of the genetic change from sire progenies and fr dam progenies would have been very different, but with the regress adjustment the estimates were quite similar. Finally, any maternal age effe will have little or no effect on the estimates of genetic change calculated fr sire progenies but they will affect the estimates calculated from dam progen If the effect of increasing maternal age is to increase progeny backfat thi ness then the genetic improvement will be overestimated here, whereas will be underestimated if progeny backfat thickness decreases with increas maternal age.

A genetic change equal to the observed change in backfat thickness wo have been quite feasible by testing and selecting, using the best 10–2 of progeny tested sires and the best 20–30% of dams as parents of the n generation. But though feasible was it in fact achieved? Were the selecti differentials sufficiently large to accommodate the rapid change? To prov a genetic change of –0·71 mm. per year in backfat thickness the aver

selection differential for both sires and dams of future breeding stock must be at least −1·6 mm., taking the generation interval as 2·25 years. Since the accuracy of selection will be far from perfect this is quite a conservative figure. However, from the annual reports, the average superiority over their contemporaries of sires entering the herd book, the élite sires, was only about 1·0 mm. Their mates are even less likely to be intensely selected since most of the sows at the breeding centres are homebred. More direct evidence on the selection of parents for breeding stock is given by J. W. B. King (personal communication) who found that the sires of a sample of 150 young boars first tested in 1959 had 1·0 mm. less backfat than their contemporaries. He concluded that unless breeders were using criteria other than the progeny test reports to aid their selections the observed change was much greater than the predicted genetic change.

It is often implied in progeny testing that where the conditions of housing and feeding are closely standardised over the years, all changes in performance must be genetic in origin. But though the control may be partial it can never be complete and some of the observed change may be environmental change. Thus it is estimated here that environmental change made up about four-fifths of the total change in backfat thickness, though there is no evidence on the kinds of environmental change involved.

Though the results of each of the separate analyses given here may not be sufficiently critical on their own, taken together they support the general conclusion that the genetic change in backfat thickness was much smaller than the observed change. Thus in the initial analyses only small differences were found between the contemporary progeny from parents of different ages but there were large differences between the progeny in different years from parents of a particular year of birth class. Intense selection among parents in each year would be expected if these results were consistent with a large genetic change. However, the selection differentials among parents in each year were not large and in fact, dams with fatter than average progeny were retained and retested in subsequent years. The estimates of genetic change derived by comparing the progeny of particular parents, and particular matings, in consecutive years were in general agreement with one another. They indicated that there was some genetic improvement in backfat thickness in the breed from 1952 to 1960 but that this accounted for only about a fifth of the observed change.

The popular uncritical acceptance of genetic change in performance equal to the observed change in the Danish Landrace breed is thus seriously challenged, for what may apply to one trait may also apply to others. The challenge is likewise extended to all other livestock improvement schemes which make no provision to measure genetic change but rely on the observed change in performance to measure their effectiveness.

SUMMARY

Data from the Danish progeny test reports were used in an attempt to measure the genetic change in backfat thickness in the Danish Landrace breed from 1952 to 1960. Over this period the average backfat thickness of tested pigs fell from 34·2 mm. to 28·5 mm., a change of two standard deviation units.

The method used to measure genetic change depends on the difference

in performance in two or more years of progeny from particular sire dams. Environmental differences between the years are avoided by measu performance relative to the year mean. However, allowance has to be m for selection among parents on the basis of their first set of progeny reco through adjusting the initial records by theoretical regression factors. genetic change is then estimated as a function of the difference betwee adjusted first progeny records and the records of subsequent progeny gro

Separate estimates of the genetic change in backfat thickness were culated in this way from the progenies of sires and of dams at each of three stations. These were in general agreement and indicated that t was some genetic improvement in backfat thickness in the Danish Land from 1952 to 1960 but that not all of the observed change was genetic cha The overall estimate of the genetic change was $-0{\cdot}15 \pm 0{\cdot}10$ mm. per and this represented about one-fifth of the observed change. Other critical results are also given and these lead to the same general conclu

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THE USE OF SPECIALISED SIRE AND DAM LINES IN SELECTION FOR MEAT PRODUCTION

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THE traits involved in meat production can be divided into two groups, (i) those concerning reproductive performance in the dam and (ii) those representing growth and carcass characteristics in the progeny. The first aspect involves adult females while the other relates to young meat animals whose reproductive performance is of no consequence. This separation of the function of the dams and their progeny in meat production is often exploited in practice by using different breeds or lines as the male and female parents.

In this paper the rates of improvement by selecting for overall performance in a single line are compared in some rather simple situations with the rates of improvement by selecting in specialised dam and sire lines which are subsequently crossed. The dam line is selected for number of offspring produced and the sire line for growth and carcass traits. A common intensity of selection is taken for all lines. Performance on crossing is treated additively as the sum of the contributions of the parental lines.

SELECTION PROCEDURE

In calculating the expected rates of genetic improvement in each of the lines, the formulae are much more tractable if overall performance is restricted to two components, X_D representing reproductive performance and X_S representing the performance of the progeny. These can denote either a single major trait or an index of several traits involved in each component. It is convenient to express both X_D and X_S in standard deviation units so that their phenotypic variances are unity. Let h^2_D and h^2_S be the respective heritabilities and let r and g represent the phenotypic and genetic correlations between the two traits. For every performance in X_D in the population there will be n performances in X_S, n being the number of offspring per dam. This difference can be taken into account by defining the relative economic value (a) as the value of one standard deviation change in X_D relative to the value of n standard deviations change in X_S. The various parameters can be combined in a selection index (e.g. Hazel, 1943) which will maximise the genetic improvement towards some specific goal. The goal is defined by an aggregate breeding value (G), a linear function of the breeding values G_D and G_S for the two traits.

The aims of selection will vary in the different lines. In selecting a single line for overall performance the aim is to maximise the change in aG_D+G_S, while in a sire line and in a dam line the goals are to improve G_S and G_D respectively. However, a mother contributes half the genes of her crossbred progeny and a more appropriate goal in selecting a dam line is $aG_D+\frac{1}{2}G_S$.

Whatever the aim of selection, a selection index combining information on both traits will provide maximum genetic gains. Howe while individual performance in X_S is likely to be available for all anim early in life, individual performance in X_D can only be measured in one after some period of reproductive life. To provide an index which is cal able for *all* animals at *one* stage, X_D is taken to be the reproductive perfo ance of the individual's dam. In selection this also allows the same ge ation interval and the same intensity of selection to be assumed for lines. The intensity of selection possible will, in fact, be a function of reproductive capacity of the species and should be roughly comparable all lines. The selection index then is $b_S X_S + b_D X_D$ where X_S and X_D measured on the individual and on its dam respectively. The losses efficiency by selecting a sire line exclusively on X_S and a dam line only X_D, rather than on an index, are also considered.

The normal equations for deriving the selection indices are:—

$$b_S + rb_D = \text{Cov } X_S G$$
$$rb_S + b_D = \text{Cov } X_D G$$

where r is the phenotypic correlation between a dam's performance in and her offspring's performance in X_S, and G is the aggregate breeding v selected for. The selection indices are of the form $(1-rk)\ X_S + (k-r)$ where $k = \text{Cov } X_D G / \text{Cov } X_S G$.

The expected improvement from selection on the index can be algebraically into the change in G_S and the change in G_D. The total provement in the various breeding schemes was taken as the sum of half change in G_S in both the sire and dam lines plus a times the change in the dam line.

Since it is the relative rates of improvement by the different bree schemes, rather than the absolute rates, that are required, only the rel heritabilities and the relative economic values of the two traits need be sidered. A range of values was specified for these and the relative rat improvement in overall performance by the different breeding schemes calculated. The range of parameters chosen to represent the two sets of were:—

(i) ratio of the heritabilities: $h_D^2/h_S^2 = p$
5, 2, 1, 0·5, 0·2
(ii) relative economic value: a
5, 2, 1, 0·5, 0·2
(iii) genetic correlation: g (favourable if positive)
0·8, 0·5, 0·2, 0·0, −0·2, −0·5, −0·8.
(iv) phenotypic correlation: r
0·4, 0·2, 0·1, 0·0, −0·1, −0·2, −0·4.

Computation of the estimated genetic improvement obtained by possible breeding schemes, detailed in Table 1, was made for the combinations of the above parameters using a Ferranti Sirius comp [Note that the genetic correlation (g) refers to the breeding values G_D G_S in the same individual, while the phenotypic correlation (r) refe X_D in a dam and X_S in her progeny. Thus $r = e\sqrt{(1-h^2_D)(1-h^2_S)} + \frac{1}{2}g\sqrt{h^2_D\, h^2_S}$, where e is the environmental correlation between X_D in a

and X_S in her progeny. Certain combinations of the parameters h^2_D, h^2_S, g and r will not be possible in practice (e.g. Searle, 1961), and some of the results may therefore represent impossible cases. It turns out, however, that the value of r has only a minor effect on the relative efficiencies of the different breeding schemes and the value $r = \frac{1}{2}g$ was chosen for tabulation in Table 2.]

RESULTS

Firstly a comparison is made of the relative rates of improvement by (i) selecting for overall performance in a single line and by (ii) selecting in the

TABLE 1

The various breeding schemes investigated

			Male parent selected for: aG_D+G_S using an index of X_S and X_D	Male parent selected for: G_S using an index of X_S and X_D	Male parent selected for: G_S using X_S
Female parent selected for:	aG_D+G_S	using an index of X_S and X_D	Case 1	Case 2	Case 3
	$aG_D+\frac{1}{2}G_S$	using an index of X_S and X_D		Case 4	Case 5
	G_D	using an index of X_S and X_D		Case 6	Case 7
	G_D	using X_D		Case 8	Case 9

X_D = phenotype for reproductive performance.
X_S = phenotype for progeny performance.
G_D = breeding value for reproductive performance.
G_S = breeding value for progeny performance.
a = relative economic value.

two specialised lines by the best procedure. Secondly the losses in efficiency incurred by alternative methods of selecting the sire and dam lines are studied.

Among the various breeding schemes studied the greatest rate of improvement always came by the procedure shown in case 4, Table 1, that is by selecting specialised sire and dam lines each on an appropriate index. The efficiency of this procedure, relative to selection in a single line (case 1), is tabulated in the first half of Table 2. Selecting specialised lines in this way is never less efficient than selecting a single line and may be much more efficient in certain cases.

When the genetic correlation between the two traits is favourable, so that changes in them are compatible, the gains in efficiency from selecting specialised lines are rather marginal. But if the genetic correlation is low or

TABLE 2

The rate of improvement by selecting in specialised sire and dam lines, relative to selecting in a single line (case 1 = 100)
(i) case 4, (ii) case 9 (see Table 1)

			(i)							(ii)				
			g †							g				
a	p	ap ‡	0·8	0·5	0·2	0·0	−0·2	−0·5	−0·8	0·8	0·5	0·2	0·0	−0·2
5	5	25	100	101	103	104	105	107	109	94	97	102	104	105
2	5	10	100	102	105	108	112	119	126	93	97	102	108	112
5	2		100	102	105	108	112	117	118	78	88	102	108	112
1	5		100	103	108	113	121	141	166	92	96	105	111	120
2	2	4–5	100	103	108	115	124	146	160	79	87	101	112	124
5	1		100	102	107	113	122	134	131	63	77	97	111	120
0·5	5		100	103	109	115	126	166	308	91	93	102	109	121
1	2	2–2·5	100	102	108	114	126	171	302	79	84	96	106	121
2	1		100	102	107	114	129	180	233	65	75	91	106	128
5	0·5		100	101	106	115	137	171	154	49	63	87	109	137
0·2	5		100	102	105	108	112	118	114	88	87	89	89	90
0·5	2		100	102	105	108	113	127	161	78	80	85	89	96
1	1	1·0	100	101	104	108	114	141	306	66	72	81	89	102
2	0·5		100	101	104	108	118	191	515	54	63	76	89	110
5	0·2		100	100	103	108	131	308	229	39	50	68	89	130
0·2	2		100	101	101	102	102	102	101	78	74	71	69	66
0·5	1	0·4–0·5	100	101	102	103	104	106	105	68	69	71	73	75
1	0·5		100	101	102	103	104	110	134	57	62	68	73	79
2	0·2		100	100	101	102	103	114	228	45	52	61	69	79
0·2	1		100	100	100	100	101	100	100	69	65	62	60	57
0·5	0·5	0·2–0·25	100	100	101	101	101	101	100	60	61	61	62	63
1	0·2		100	100	100	100	101	101	101	50	54	57	60	63
0·2	0·5	0.1	100	100	100	100	100	100	100	62	60	57	55	53
0·5	0·2		100	100	100	100	100	100	100	53	54	55	55	55
0·2	0·2	0·04	100	100	100	100	100	100	100	55	55	53	52	51

† Phenotypic correlation (r) taken as half the genetic correlation (g) (see text).
‡ a = relative economic value.
p = ratio of the heritabilities, h^2_D/h^2_S.

unfavourable, so that the change in one trait is unaffected or tends to reduced by changes in the other, fairly substantial gains in efficiency can obtained by selecting in specialised lines. Increases of 15–50% in the e iency of improvement are commonly obtained while in certain cases efficiency may be five times as great.

A pattern of the efficiency of improvement from using specialised li is not evident either for the ratio of the economic weights (a) or for the r of the heritabilities (p). However, there is a good agreement among efficiencies for the value of the product ap, as shown by the groupin

Table 2. If the product is intermediate (between 1 and 5) there may be gains in the efficiency of improvement by using specialised lines. On the other hand where the balance between a and p is lacking the gains in efficiency are not worthwhile and a single line will suffice. Why is this so? In the context of a single line the quantity ap measures the economic improvement by selecting for one character relative to the improvement by selecting for others. If ap is large or very small all the selection in the specialised lines will swing to one of the traits and effectively ignore the other and there will be no gain in efficiency over selecting in a single line. On the other hand where ap is intermediate the fruits of selection for the two characters are equivalent and specialised lines can make use of the different functions in dam and progeny performance, especially if these are incompatible in a single line.

As stated earlier, the value of the phenotypic correlation between X_D in a dam and X_S in her progeny is not critical in affecting the pattern of the efficiencies in the results. Within each combination of a, p and g, the efficiency of improvement by specialised lines tends to be reduced slightly as the phenotypic correlation turns negative, more so when the genetic correlation is also negative and ap lies in the intermediate range, but these are the very conditions when the benefits of using specialised lines are large anyway.

What losses in the rate of improvement are incurred by simplifying the selection procedures in the specialised lines? If the sire line is selected on X_S (case 5, Table 1), rather than on an index (case 4) the rate of improvement is only slightly reduced. A dam line selected for the same criteria as the single line (cases 2 and 3) provides the same rate of improvement as the optimum procedure (case 4), except when the efficiency is already high. On the other hand, if G_S is ignored in selecting the dam line, whether selection is on an index (cases 6 and 7) or exclusively on X_D (cases 8 and 9), the rate of improvement can be reduced. The efficiency for case 9 relative to case 1 is given in the second half of Table 2. If the genetic correlation is favourable or the product ap is less than one, the rate of improvement in such specialised lines may fall far short of the rate of improvement in a single line. Even for negative genetic correlations and ap values greater than one, there are still likely to be large losses in efficiency compared with the optimum procedure (case 4). In short, some consideration must be given to traits of progeny performance in selecting a dam line.

DISCUSSION

There is something of a paradox between the use of specialised lines that already exist and the development of new specialised lines by selection. The latter depends on planned selection efforts in the future while the former capitalises on the range of lines currently available. In the initial stages of a breeding programme the greatest immediate gains are likely to come from selecting *among* lines (breeds, strains) and *among* possible line crosses. To avoid testing some large number of crosses a reasonable procedure is to take cross performance as the average of the two parental lines. This should be satisfactory for traits of high heritability (Donald, 1955), such as efficiency of feed conversion and carcass traits, but it may be less suitable for reproductive performance which often shows a substantial degree of heterosis on crossing. Though the best crossing lines and the best specific crosses can be found only by testing, some weight can be given in prediction to the enhanced reproductive performance of crossbreds by assigning an average effect to the parental

average for all crosses. A ranking for overall merit of an array of lines and crosses can then be attempted taking into account the actual or predicted performance for each trait and its relative economic weight. A shortened list of lines and crosses can then be selected for further testing.

Can any generalisations be made about the optimum choice among lines and their crosses? If cross performance is again taken as the average of the two parents (plus an assigned effect if heterosis is expected) the best combination of lines can be chosen in an approximate manner. Using the symbols X_D and X_S as before, except that they now refer to the mean performance of a line rather than the individual, the female parent will contribute $aX_D+\frac{1}{2}X_S$ and the male parent adds $\frac{1}{2}X_S$. No matter what line or cross is used as the female parent, the best male line adds the maximum value of X_S and, unless there is some intermediate optimum in performance, will maximise the economic merit of the progeny. Similarly the female parent having the largest value of the expression $aX_D+\frac{1}{2}X_S$ will maximise overall performance. Evaluation of lines by this procedure should serve to screen the various lines and line crosses.

Having chosen the best line or line combination the problem changes to selection within lines and to a comparison of the rates of improvement that different breeding schemes afford. Here again it has only been possible to deal with a rather simple set of assumptions and conditions. Thus selection has been restricted to two components, though each may represent several traits. In order to have an index value for all individuals at a given stage, selection is based on the reproductive performance of an individual's dam and on its own performance for growth and carcass traits. This is convenient because the same intensity of selection and the same generation interval can then be applied to both sexes and all lines. Though convenient, this assumption may be somewhat artificial. If the specialised lines are half as large as the single line they may have more restrictions on selection to minimise inbreeding. Alternatively, two lines may be selected concurrently for overall performance and the better of the two subsequently chosen. In both cases any advantage of using specialised lines might be reduced. Another restriction follows from using a selection index in that only the additive genetic variation is considered. Moreover, in combining the lines the expected gains from selection have been treated additively. These may be important limitations when some of the value of maintaining specialised lines in practice depends on heterosis in the crossbred progeny. Selection for crossbred performance would, however, alter both the intensities of selection and the criteria for selection and therefore is outside the context of this paper.

The present results may be of most value in indicating the situations where selection in specialised lines may lead to faster genetic gains. First they indicate that by selecting in specialised lines the rate of improvement need never be less and may be considerably greater than by selecting for overall performance in a single line. Where the ratio of the heritabilities and the ratio of the economic weights of the two traits show a certain balance with one another, handsome gains in the rate of improvement can be obtained. The more unfavourable the genetic correlation between the two traits the more efficient does the selection in specialised lines become. It seems that in selecting specialised sire lines reproductive performance can be conveniently ignored. On the other hand, substantial losses in efficiency may

result if the selection in dam lines does not take account of growth and carcass traits as well as reproductive performance.

Are the conditions which favour selection in specialised lines likely to be met in the various meat producing species of farm animals? The heritabilities of traits measuring reproductive performance tend to be low (10–15%).

TABLE 3

Estimation of the product (ap), the relative economic value (a) times the relative heritability (p) of reproductive performance (number of offspring) and offspring performance (efficiency of feed conversion), for five types of meat animal

		Heritability %	$p = h^2_D/h^2_S$	No. of offspring	Standard deviation (coeff.-var 25%)	Value of one offspring (shillings)	Live-weight gain (lb.)	Feed efficiency (lb. food/lb. gain) †	Standard deviation (coeff.-var 8%)	Cost per 100 lbs. of food (shillings) †	Value of one standard deviation change (shillings)	Relative economic value (*a*)	*ap*
ICKEN (BROILER)	No. offspring	10	0·25	100	25	1·25					31	1·2	0·30
	Feed efficiency	40					3·5	2·6	0·21	36	26		
RKEY	No. offspring	10	0·25	30	7·5	6·7					50	1·0	0·25
	Feed efficiency	40					20	3·0	0·24	33	48		
(PORK)	No. offspring	10	0·33	8 ‡	2·0	80 §					160	3·3	1·00
	Feed efficiency	30					100 ‖	3·0	0·24	25	48		
(BACON)	No. offspring	10	0·33	8 ‡	2·0	80 §					160	2·0	0·67
	Feed efficiency	30					160 ‖	3·4	0·27	23	80		
F CATTLE	No. offspring	10	0·25	1	0·25	500 §					125	3·8	0·95
	Feed efficiency	40					500 ‖	4·0	0·32	21	33		

† Concentrate rations.
‡ Per litter.
§ At weaning (less extra feed cost).
‖ Weaning to slaughter

while traits of progeny performance such as efficiency of feed conversion and carcass traits have higher heritabilities (30–60%). The ratio of these figures (*p*) will generally be less than 0·5. The ratio of the economic weights (*a*) for the two components of performance is more difficult to assess. However two figures which are usually known are the value of each offspring at birth, or weaning, and the cost of the ration. By using the number of offspring to represent reproductive performance and efficiency of feed conversion to represent progeny performance, a value for (*a*) can be calculated. To some extent this value may be regarded as a maximum value for the ratio, for while the number of offspring produced largely summarises reproductive performance, efficiency of feed conversion represents only part of the progeny performance, carcass traits also being relevant. Details of the statistics used

to provide some guide to the values of *ap* for different species are given Table 3. In the larger farm animals the milking ability of the dam large determines the early growth of her offspring and it is difficult to separate maternal and offspring effects. This is the case for sheep and since most lambs are sold for slaughter at weaning, no value of *ap* has been derived for lamb production. However, pigs and beef cattle have a substantial post-weight gain between weaning and slaughter and the feed efficiency during this period can be set against the dam's performance measured at the weaning of her offspring.

Though the ratios of the economic values are rather approximate, it appears that the values of *ap* lie between 0·25 and 1·25 in the different species. The critical levels for *ap* (see Table 2) are the intermediate values falling between 1 and 5. Since the estimated values of *ap* lie well outside this range for broilers and turkeys, it would appear that the rate of improvement using specialised lines in these species is likely to be no better than that in a single line. Selecting in specialised lines that already exist can only be expected to maintain their position relative to other lines similarly selected, and development of new specialised lines would not appear to be worthwhile. The estimates of *ap* in the larger farm animals lie around the lower levels of the critical range. Even here, only if there is an unfavourable genetic correlation between reproductive performance and growth and carcass traits will selection in specialised lines add much to the rate of improvement in performance. On the other hand, from the values of *ap* estimated for the different species it is clear from the second half of Table 2 that selecting a dam line exclusively for reproductive performance may lower the overall rate of improvement considerably.

SUMMARY

Progress by selecting in a single line for overall merit is compared with the progress by selecting and crossing specialised sire and dam lines. The sire line is selected for growth and carcass traits, the dam line for number of offspring produced. The rate of improvement through specialised lines is never less than that in a single line and can be considerably greater but only if there is an unfavourable genetic correlation between progeny number and performance and if there is a certain balance between the heritabilities and economic weights of the two sets of traits. In a sire line the selection may ignore progeny number without loss in efficiency but in a dam line progeny growth and carcass performance must be considered in addition to the number of offspring or else substantial losses in the efficiency of improvement may be suffered.

From estimates of the relative economic weights and relative heritabilities of number of progeny produced and the efficiency of feed conversion in several meat species it was concluded that selecting in specialised lines would have little advantage over selecting for overall performance in a single line.

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CROSSBREEDING AND LITTER PRODUCTION IN BRITISH PIGS

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THERE is an extensive literature on the results of crossbreeding in pigs with reports covering a wide variety of breeds and environmental conditions. An improvement of litter production on crossbreeding is well established by this literature (e.g. Fredeen, 1957). The present report concerns perhaps the most extensive analysis yet on the subject, dealing with records of purebred and crossbred litters taken on farms in Britain. The main topics studied are the overall litter performance of purebreds and crossbreds, both as piglets and as dams, and the merit of different purebreds and crossbreds in their litter production. The contributions of farm differences and of farm by breeding-group interaction to the total variation in litter production are assessed, and the variation within purebred and within crossbred groups is compared.

MATERIAL AND METHODS

Data on farm litter records were obtained from the Pig Industry Development Authority in Great Britain, for each of the four six-monthly recording periods from April 1959 to March 1961. The litter records were taken by the farmers, subject to check weighings by recording officers. They were then collected, standardised for age and processed by a central office. All records from farms having more than one breed of boar, or more than one breed or breed cross of sow, were selected and over 8,000 litters from about 500 farms were obtained in each period, making a total of some 34,800 litters. The breed of the boar (only purebred boars are licensed for breeding) and breeding of the sow were known for each litter. Summaries were prepared for selected breeding classifications within farms for each of the four periods, and details of each litter were available for the second and third six-monthly periods.

The greater part of the data involved the Large White (LW) and Landrace (L) breeds and their crosses, as shown in Table 1, and a large proportion of the litters from crossbred sows were backcrosses to one of these breeds.

The sixteen different breeding groups and farms made up a two-way classification with unequal subclass numbers and with only 18% of the cells of the two-way table filled. Taking farm effects as random and the breeding groups as specified or fixed, a least squares analysis was performed as outlined by Searle and Henderson (1961) for a mixed model. This analysis is roughly equivalent to comparing the breeding groups within farms and weighting the comparisons in proportion to the information they provide. There was no apparent disproportionality between purebred and crossbred litters within farms for several factors examined such as length of farrowing index, proportion of gilts and details of husbandry (for example whether the litters were born and reared indoors or outdoors). Analyses were made within each of the four recording periods and their results pooled it being assumed that

about 50% of sows were common to consecutive periods and that the repeatability of traits measuring litter performance was 0·15 (Lush and Molln 1942).

In estimating components of variance large sampling errors were expected to arise from a high proportion of empty cells and unequal numbers in the subclasses of the two-way table (Searle, 1961). The number of breeding groups was thus condensed to the three main groups in Table 1, whereupon

TABLE 1

The percentage of litters in sixteen designated breeding groups

Purebred	%	Single † cross	%	Backcross and three-breed cross †	%
Large White (LW)	27·4	LW×L	2·8	LW×(LW×L)	0·9
Landrace (L)	20·4	L×LW	8·6	L×(LW×L)	1·5
Wessex (Wx)	7·5	LW×Wx	4·1	LW×(L×LW)	0·9
Other	2·1	L×Wx	4·2	L×(L×LW)	1·7
		Other	2·3	LW or L×(LW×Wx)	0·8
				LW or L×(L×Wx)	0·9
				Other	13·9
Total	57·4		22·0		20·6

† Breed of boar first.

70% of the cells were filled, and components of variance were estimated from a similar analysis of the condensed data.

The following traits were chosen for analysis:—

Number of pigs born alive
Number of pigs alive at 3 weeks
Number of pigs alive at 8 weeks (weaning)
Litter weight at 3 weeks
Litter weight at 8 weeks

Although these traits are highly intercorrelated they do reflect somewhat different aspects of litter production, namely prolificacy of the sow, ability of piglets to survive, and total litter production. The analyses at each stage were made among all litters then present. Sows which had no live piglets may or may not have been recorded at birth on different farms. Of those recorded at birth, 6% were absent subsequently. These might have lost their litters or may have passed unrecorded for some other reason at 3 weeks and 8 weeks.

RESULTS

Mean performance of purebred and crossbred litters

The estimates of litter performance in the sixteen breeding groups were quite similar in the four periods and the pooled results are presented in Table 2. Among the purebreds the performance of Large White sows was outstanding for number of piglets born alive. However, their piglets had a higher early mortality than the other purebreds and at weaning the total litter weights were similar. When purebred sows were mated to produce crossbred litters their litters were larger but the breeds were in the same ranking at farrowing. The crossbred piglets subsequently survived better and were heavier than

purebreds at weaning, and by then there was little to choose among the various crosses. On average, crossbred dams were as good as purebred Large White sows in their farrowing performances, but there was less mortality among their piglets, and they weaned substantially heavier litters.

Table 2 gives the ranking of the breeds and crosses in their litter performance and also indicates the general improvement on crossbreeding. The extent of the heterosis is hard to gauge however, since all groups are compared to the Large White breed. In Table 3, the performance of crossbred and purebred litters from the same breed of sow are compared and the

TABLE 2

Litter performance of sixteen breeding groups (as deviations from the performance of purebred Large White litters) with standard errors

Breeding group		Number born alive		Number at 3 weeks		Number at 8 weeks		Litter weight at 3 weeks (lb.)		Litter weight at 8 weeks (lb.)	
Boar	Sow	Mean	S.E.	Mean	S.E.	Mean	S.E.	Mean	S.E.	Mean	S.E.
Large White (LW)	LW	10·7		8·8		8·5		108		306	
Landrace (L)	L	−0·74	0·07	−0·06	0·06	−0·33	0·06	1·0	0·8	5	2
Wessex (Wx)	Wx	−1·00	0·10	−0·27	0·08	−0·30	0·09	2·5	1·1	−3	3
Other purebreds		−0·92	0·17	−0·43	0·14	−0·42	0·15	0·1	1·9	10	6
LW	L	−0·32	0·12	0·15	0·10	0·22	0·10	8·0	1·4	40	4
L	LW	−0·02	0·08	0·14	0·07	0·21	0·07	4·2	0·9	25	3
LW	Wx	−0·61	0·12	0·31	0·10	0·36	0·10	9·1	1·3	34	4
L	Wx	−0·64	0·09	−0·05	0·10	0·00	0·10	6·0	1·3	27	4
Other single crosses		−0·53	0·14	0·11	0·12	0·15	0·12	4·9	1·5	19	5
LW	(LW×L)	0·17	0·19	0·61	0·16	0·65	0·16	12·2	2·1	36	6
L	(LW×L)	−0·25	0·17	0·05	0·14	0·20	0·15	5·1	1·9	25	6
LW	(L×LW)	0·66	0·19	0·87	0·16	0·88	0·16	13·5	2·1	43	6
L	(L×LW)	−0·25	0·15	0·03	0·13	0·11	0·13	7·0	1·7	21	5
L or LW	(LW×Wx)	0·07	0·24	0·69	0·20	0·78	0·20	10·7	2·6	45	8
L or LW	(L×Wx)	−0·25	0·20	0·15	0·16	0·20	0·17	7·7	2·2	30	7
Other crossbreds		−0·05	0·08	0·26	0·07	0·01	0·07	8·3	0·9	31	3

superiority of the crossbred sows over the average purebred performance of the parental breeds is presented. The general conclusions are the same as before. The degree of heterosis for traits measuring litter production ranged from about 2% to 11%, increasing generally with the age of the litter and being higher for litter weights than numbers per litter. For the latter the heterosis of litters from crossbred sows was double that of crossbred litters from purebred sows, but the difference was much smaller for litter weights. In this comparison a large proportion of the litters from crossbred sows were backcrosses. Unfortunately there were too few three-breed cross litters available to compare with the single cross and backcross litters.

Variability among purebred and crossbred litters

The variation in litter performance within the sixteen breeding groups within farms was measured using the detailed records of the second and third

periods. Since the pattern of variation was rather inconsistent the variance were condensed into three main groups weighting each variance according to its degrees of freedom. The pooled within group variances are shown in Table 4.

TABLE 3

Comparison of the litter performance (a) of crossbred and purebred litters from the same breed of sow and (b) of crossbred sows with the average purebred performance of the parental breeds (with standard errors)

	Number born alive		Number at 3 weeks		Number at 8 weeks		Litter weight at 3 weeks (lb.)		Litter weight at 8 weeks (lb.)	
	Mean	S.E.	Mean	S.E.	Mean	S.E.	Mean	S.E.	Mean	S.E.
(a)										
Crossbred litter – purebred litter										
breed of sow LW	−0·01	0·08	0·14	0·07	0·21	0·07	4·2	0·9	24·7	2·
breed of sow L	0·42	0·13	0·49	0·10	0·55	0·10	7·0	1·4	34·3	4·
breed of sow Wx	0·37	0·11	0·40	0·09	0·48	0·09	5·1	1·1	33·0	3·
Average difference	0·26		0·34		0·41		5·4		30·7	
Average superiority (%)	2·2		3·9		4·8		5·0		10·0	
(b)										
Crossbred sows – average of parental purebred sows										
(LW×L)&(L×LW)	0·46	0·10	0·56	0·08	0·62	0·08	9·0	1·0	28·2	3·
(LW×Wx)	0·58	0·24	0·83	0·20	0·93	0·20	9·4	2·6	46·5	7·
(L×Wx)	0·63	0·20	0·45	0·16	0·52	0·16	7·0	2·1	28·6	6·
Average difference	0·56		0·61		0·70		8·5		34·4	
Average superiority (%)	5·2		6·9		8·2		7·9		11·2	

TABLE 4

Mean squares and coefficients of variation within farms among purebred and crossbred litters

	Purebred litters		Crossbred litters from purebred sows		Litters from crossbred sow	
	M.S.	C.V.	M.S.	C.V.	M.S.	C.V.
Number born alive	7·17	26	7·05	25	7·63	26
Number at 3 weeks	4·85	26	4·78	25	4·77	24
Number at 8 weeks	4·95	27	4·56	24	4·84	24
Litter weight at 3 weeks (lb.)	863	27	763	24	757	24
Litter weight at 8 weeks (lb.)	7624	28	7053	25	7344	25

With one exception the purebred litter group was the most variable for all five traits. Crossbred litters from purebred sows were slightly less variable than litters from crossbred sows. However, the largest category of crossbred sows included a number of the less common crossbreds and crossbred sows of unknown breeding and so the litters from crossbred sows may appear more heterogeneous for these reasons.

Components of variation in litter performance

As already mentioned, in estimating components of variance the data were condensed into three composite groups. For comparison of the two analyses the mean performances of these groups are given in Table 5. Being composite breeding groups, their performance depends on the proportions of different breeds and breed crosses involved. About half of the sows producing purebred litters were Large Whites and consequently the two other groups showed less superiority than was found in the previous analysis for numbers per litter, but differences in litter weights were less affected.

In the analysis of variance, farm by breeding group interactions were highly significant for all traits in all periods. With such an extensive set of

TABLE 5

Litter performance of three composite breeding groups (as deviations from the performance of purebred litters) with standard errors

	Purebred litters	Crossbred litters from purebred dams		Litters from crossbred dams	
		Mean	S.E.	Mean	S.E.
Number born alive	10·3	0·19	0·03	0·44	0·03
Number at 3 weeks	8·6	0·31	0·03	0·48	0·03
Number at 8 weeks	8·4	0·36	0·03	0·56	0·03
Litter weight at 3 weeks (lb.)	108	5·5	0·30	8·2	0·40
Litter weight at 8 weeks (lb.)	308	26·7	1·0	29·1	1·1

TABLE 6

Percentages of the variation in litter performance attributable to different sources

	Farms	Farm by breeding group interaction	Remainder
Number born alive	8·8	1·3	89·9
Number at 3 weeks	8·4	1·3	90·4
Number at 8 weeks	9·6	1·1	89·4
Litter weight at 3 weeks	15·7	1·4	82·9
Litter weight at 8 weeks	23·4	1·3	75·3

data such a result is not surprising and the relevant question is not whether interaction effects exist but how important they are in affecting litter performance. The components of variance for farms and for farm by breeding group interactions estimated in the four periods were in good agreement and their average is presented in Table 6.

The interaction component, though highly significant, contributed only from 1·1% to 1·4% of the variation in litter performance. The variation due to farm differences was far greater, especially for litter weights.

DISCUSSION

Crossbreeding plays an important role in commercial pig production in Britain and the practice is well supported by the findings in this paper. In fact over 60% of the $1\frac{1}{4}$ to $1\frac{1}{2}$ million litters produced annually are crossbred and some 70% of these are from crossbred sows (P.I.D.A. survey, 1961).

Despite the extent of the practice there is no well-defined pattern in crossbreeding as found in the criss-crossing or rotational crossing of several breeds in the U.S.A. or in the stratification of breeds and crosses seen the sheep industry in Britain.

The enhanced litter performance through crossbreeding found in Britis pigs is in general agreement with the numerous reports on crossbreeding in literature dealing with a wide variety of breeds and environmental conditio Reviews by Fredeen (1957) and Lauprecht (1957), summarise the m American and European contributions respectively. More recent repo by Gaines and Hazel (1957), Cobb (1958), Koh (1958), Skårman (19 and (1961b), Willham (1960), Kabanov (1961) and others all support findings of earlier workers. Surprisingly in this extensive literature crossbreeding, comparisons of contemporary purebred and crossbred s are rather sparse. In this paper and in Skårman (1961b) the litters fr crossbred sows were backcrosses to one of the parental breeds and thus m show less hybrid vigour than three-breed cross litters. Results for performance of crossbred sows producing three-breed cross litters seem be restricted to two reports, an early paper by Winters *et al.* (1935) and abstract of Gaines and Hazel (1957). These do seem to indicate a grea gain from the three-breed cross litters but different breeds and conditi were involved.

Though a difference in variability was found among purebred and cr bred litters it would be too small to be discernable in practice. When difference in mean performance is also taken into account the frequenc litters of different sizes in the purebred and crossbred classes will di rather more. However when dealing with small numbers of litters un varying farm conditions the differences in frequency would still be diffi to detect. The proportion of variation due to farms shows that farm envir ment had a considerable effect on litter performance. Since the breed groups were scattered disproportionately among farms, the within-far analysis was certainly justified. In fact the estimates of the superiority crossbred litters and crossbred sows from the least squares analysis were ab twice as large as those calculated from the overall averages in the P.I.D record reports. Thus it seems that farms with purebreds were provid a somewhat better environment than farms with crosses. The least squa analysis also indicates that a real breeding group by farm interaction exis but it exerted only a minor influence on these data. Thus it appears that very largely through their superior mean performance that crossbred lit and crossbred sows excel in litter production.

SUMMARY

The litter production of various purebred and crossbred groups of were studied in data collected from 1959 to 1961 on some 34,800 lit recorded on over 800 farms in Britain. A least squares analysis was formed to obtain within-farm estimates of performance for five litter trait sixteen specified breeding groups and to analyse the total variation in li performance.

The ranking of the purebreds and crossbreds is presented. In gene there was a lower mortality in crossbred litters which had 2% more pig birth and 5% more pigs at weaning than purebred litters. The total li

weight at weaning was 10% greater in crossbred litters. Crossbred sows showed more heterosis with 5% more pigs at birth, 8% more pigs at weaning and an advantage of 11% in total litter weight at weaning.

Farm differences accounted for a major portion of the total variation in litter production, 8–9% for litter numbers and 15–25% for litter weights. On the other hand the interactions of farms and breeding groups, though highly significant, contributed only 1–2% of the total variation in litter production.

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RESULTS OF PIG PROGENY TESTING IN GREAT BRITAIN

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A NATIONAL pig progeny testing service has been available to pig breeders in Great Britain since 1958 and an extensive set of test results has accumulated. These records have been used here to study what effect progeny testing has been having on pig improvement and to review the use of the testing facilities. The amount of selection based on the test results and its effect on the following generation are examined. The usefulness of the progeny test results in selecting breeding stock is examined by comparing tests on sons with tests on their parents and relating the observed regressions to their theoretical expectations. Some limitations of the system of testing and the organisation of the breeding population are discussed and proposals intended to increase the impact of testing on pig improvement are put forward.

MATERIAL AND METHODS

The data for this analysis were abstracted from the annual reports of the National Pig Progeny Testing Board (1959–63). Records were avaialble on 528 Large White boars and 294 Landrace boars tested at the five national testing stations from 1958 to 1962 inclusive. The four traits studied were daily gain, feed efficiency, average backfat thickness and carcass length. The test reports gave the boar average and the average of each of four litter groups of two castrated males (hogs) and two females (gilts) tested per boar. The pigs were individually fed to appetite, starting test at 50 lb. live-weight, and finishing test at the first weekly weighing of over 200 lb. live-weight. All the boars, their mates and their progeny were purebred. The herd of origin and full pedigree were known for all animals and it was possible to collate progeny tested boars and sows with their progeny tested sons.

The litter group records were classified by 6-month periods within stations and were adjusted to a contemporary basis by expressing performance as a deviation from the class mean. In this way differences in performance between stations and between periods were eliminated and the data could be handled as one large group without further partition or correction. The majority of boars were tested at only one station but during 1958 and 1959 some boars had progeny groups tested at more than one station. A least-squares analysis of this sub-set indicated that environmental differences accounted for most of the differences in performance between stations.

The 528 Large White boars and the 294 Landrace boars came respectively from 194 and 143 breeders. Half of these breeders tested only one boar during the 5-year period and three-quarters of the breeders tested less than four boars. With such infrequent and intermittent testing these breeders

had little opportunity for selecting among their progeny tested boars. There were some breeders who tested more frequently and thirty-seven tested more than four boars during the 5-year period. Yet, despite their greater participation in testing, the test results of pigs from these 37 breeders were only slightly better than average. The origins of the boars and their parents were traced and it was found that almost half the boars were homebred but only 15% had sires and 25% had dams which had been born on the same farm. These figures reflect the extent of the trade in pedigree stock from herd to herd and show that very few herds are closed to the introduction of new breeding stock. It is possible that there was some selection of the boars and the sows that were tested. The average age of parents, when their test litters were born was 20 months for boars and 28 months for sows. Breeders could thus have had information about growth and carcass traits for progeny of a boar and his mates before testing their litters.

RESULTS

The overall performance of the two breeds from 1958 to 1962 is given in Table 1. The trends in performance were similar in the two breeds, three

TABLE 1

Performance at the progeny testing stations from 1959 *to* 1962

Year	Daily gain (lb./day)		Feed efficiency (lb. feed/lb. carcass gain)		Average backfat (mm.)		Carcass length (mm.)	
	Large White	Landrace	Large White	Landrace	Large White	Landrace	Large White	Landrace
1958	1·53	1·51	4·22	4·31	36·1	33·7	803	810
1959	1·50	1·50	4·33	4·37	34·7	32·5	806	811
1960	1·47	1·46	4·22	4·32	33·9	32·2	804	812
1961	1·44	1·43	4·21	4·30	33·7	32·1	808	813
1962	1·46	1·45	4·16	4·27	34·7	32·6	808	813

traits showing some improvement while one, average daily gain, fell over the period. The Large White breed was consistently the more efficient in feed conversion but had shorter carcasses and thicker backfat than the Landrace.

The effectiveness of the testing depends on how much selection was practiced on the basis of test results. This was studied by comparing the progeny tests of parents having sons subsequently tested with all contemporary progeny tests. The differences in performance were then averaged, weighting by the number of sons tested. All animals tested from 1958 to 1962 with sons tested or on test at March 1964 were included. The results are given in Table 2, and show that animals with sons tested had better progeny tests than average but the superiority was not large. The selection differentials for boars (16 progeny) and sows (4 progeny) were both about 0·2 of a standard error of a test mean for daily gain and feed efficiency and about 0·4 of a standard error of a test mean for average backfat and carcass length, being larger for the Large White than the Landrace. This represents a rather mild degree of selection and would correspond to culling the poorest 5–10% of the progeny tested parents for growth rate and feed efficiency and the poorest 15–20% for average backfat and carcass length

Moreover, only a small proportion of parents in the breeding herds in the next generation have progeny tested parents, so that these selection differentials, small as they are, considerably overestimate the effect of progeny testing on the population of breeding herds as a whole. Though the four traits studied here were given priority in the test reports, results for another 14 traits were also published and some selection effort may have been spent on these.

TABLE 2

Differences between the progeny tests of parents with sons subsequently tested and all contemporary progeny tests (with the standard error of a test mean for comparison)

		Daily gain (lb./day)		Feed efficiency (lb. feed/lb. carcass gain)		Average backfat (mm.)		Carcass length (mm.)	
Performance of	Number	Difference †	S.E.	Difference †	S.E.	Difference †	S.E.	Difference †	S.E.
ars with sons tested									
Large White	166	0·01	0·05	−0·03	0·13	−1·01	2·01	6·7	10·7
Landrace	98	0·01	0·05	−0·02	0·12	−0·54	1·63	3·3	9·6
ws with sons tested									
Large White	169	0·01	0·08	−0·05	0·17	−0·96	2·32	6·1	12·3
Landrace	110	0·03	0·07	−0·03	0·17	−0·76	2·02	1·9	12·3

† Standard error of differences = standard error of test mean $\times \sqrt{\frac{2}{\text{number}}}$

The progeny test results of boars with tested parents were compared with all contemporary progeny tests. The data, in this comparison, were restricted to parents and their sons both tested in the period 1958 to 1962 and necessarily refer to parents tested early and to their sons tested later in the period. The results, in Table 3, show that the progeny tests of sons

TABLE 3

Differences in the performance of progeny from sons of tested parents and all contemporary progeny †

Performance of	Number	Daily gain (lb./day)	Feed efficiency (lb. feed/lb. carcass gain)	Average backfat (mm.)	Carcass length (mm.)
Boars with tested sires					
Large White	163	0·00	−0·01	−0·09	+1·5
Landrace	121	0·01	−0·01	+0·14	+0·7
Boars with tested dams					
Large White	98	0·00	−0·02	−0·27	+1·1
Landrace	94	0·00	−0·01	+0·01	−0·2

† Same standard error of differences, and of test means as in Table 2.

from tested parents were only marginally better than those of their contemporaries. This might have been expected in view of the small selection differentials in Table 2, but there may also have been some improvement in the untested stock in the national herd.

To determine whether parents with good test results left sons which also had good results the regressions of son's test on parent's test were calculated. However, two factors complicate the interpretation of these regressions. Parents tested in the same period had sons tested in several

periods, and vice versa. If there were genetic differences between periods, for example due to a genetic trend, these would affect the parent-son regressions. Another difficulty was that half the sons were tested from the same herd as their parents while the other half had been sold to different herds. If there were genetic differences between herds the parent-son regressions would be affected, for example if sons of high ranking parents were purchased with a view to upgrading the poor testing herds. The parent-son regressions were calculated separately for pairs tested from the same herd and for pairs tested from different herds. Any differences between herds which carried

TABLE 4

Observed regressions, with standard errors, and expected regressions of son's test on parent's test

		Father-son		Mother-son	
		Observed	Expected †	Observed	Expe
		S.E.		S.E.	
Daily gain	Large White	0·29±0·08	0·25	0·10±0·06	0·
(lb./day)	Landrace	0·13±0·08	0·26	0·09±0·05	0·
Feed efficiency	Large White	0·10±0·08	0·29	0·17±0·06	0·
(lb. feed/lb. carcass gain)	Landrace	0·14±0·10	0·29	0·14±0·05	0·
Average backfat	Large White	0·50±0·09	0·31	0·32±0·06	0·
(mm.)	Landrace	0·20±0·07	0·34	0·11±0·06	0·
Carcass length	Large White	0·42±0·08	0·30	0·33±0·07	0·
(mm.)	Landrace	0·19±0·10	0·35	0·14±0·06	0·

† Expected regressions calculated from genetic parameters of Smith *et al.* (1962) and Smith and Ross (1965).

over to affect test performance would have increased the former and reduced the latter from their expected values. In 11 out of the 16 cases the within herd regressions were the larger, indicating that the tests on sons and parent were more alike if both were tested from the same herd.

The overall parent-son regressions were also calculated, there being 159 father-son pairs and 196 mother-son pairs available. These regressions are presented in Table 4, together with expected regressions estimated from parameters of Smith, King and Gilbert (1962) and Smith and Ross (1965).

The observed regressions were all positive but tended to be larger in the Large White than in the Landrace. Agreement with the expected regressions was better for the Landrace than for the Large White in which three of the observed regressions were more than two standard errors from the expected values. However, on pooling the estimates from the two breeds the agreement between the observed and expected regressions became quite good. On the whole there seems no reason to doubt the genetic parameters obtained in earlier work especially since the observed regressions were liable to several biases in their genetic interpretation. For the same reason the parent-offspring regressions did not provide reliable estimates of heritability and moreover, in addition to the conventional genetic and residual components of variance, they involved a litter component which cannot be estimated directly from data on litter group averages.

In previous analyses with British pigs an estimate of the influence of

pre-test herd environment on the progeny test could not be obtained because so few boars were tested from any one herd. Over the 5-year period studied here, an average of 2·2 boars were tested per herd and it was possible, in an analysis of variance, to estimate a pre-test herd environment component following Jonsson and King (1962) and allowing for the genetic relationship among pigs from different sires in the same herd. Since the analysis was on the basis of litter averages, estimates of the total individual variation from previous studies were used so that the herd environment component might

TABLE 5

Genetic correlations estimated in different analyses

		Feed efficiency		Average backfat		Carcass length	
		Large White	Landrace	Large White	Landrace	Large White	Landrace
Daily gain	1 †	−0·69	−0·71	−0·03	−0·26	+0·19	+0·21
	2	−0·56	−0·54	+0·05	−0·06	+0·08	+0·10
	3	−0·75	−0·25	+0·05	−0·46	+0·00	+0·35
	4	−0·74	−0·93	−0·42	−0·43	+0·10	+0·30
Feed efficiency	1 †			+0·24	+0·44	−0·19	−0·12
	2			+0·22	+0·27	+0·02	+0·08
	3			+0·78	+0·79	−0·32	+0·24
	4			+0·75	+0·46	−0·39	−0·26
Average backfat	1 †					−0·37	−0·22
	2					−0·45	−0·01
	3					−0·47	−0·62
	4					−0·40	−0·03

† 1. Half-sib analysis—Smith *et al.* (1962)
Smith and Ross (1965)
2. Half-sib analysis—present data.
3. Parent-offspring (sire-son)—present data.
4. Parent-offspring (dam-son)—present data.

be expressed as a percentage of the total variation. The percentages in the Large White and Landrace were respectively 2% and 1% for daily gain, 0% and 1% for feed efficiency, 8% and 0% for average backfat and 5% and 0% for carcass length. The percentages for average backfat and for carcass length in the Large White were significantly different from zero and, if real, would have inflated the estimates of heritability for these traits reported by Smith *et al.* (1962).

The genetic correlations among the four traits were estimated in two ways, first from the sire components of variance and covariance in the analysis of variance and then from the parent-son covariances for each pair of traits (Hazel, 1943). The estimates are presented in Table 5 along with values found in previous analyses. There was a fair degree of agreement among the different sets of estimates though those from the parent-offspring covariances were generally the largest, for example in the correlations of feed efficiency and daily gain with backfat thickness. However, from the aspect of pig improvement it is evident that under the current market requirements

these four traits are genetically compatible and could be improved concurrently.

An attempt was made to measure the genetic change in performance with the method outlined by Smith (1962), which uses the regression of sire test performance on time as a measure of half the genetic change. However most of the sires were tested over a short interval of time and consequently the standard errors of the estimates of genetic change were rather large. The calculated genetic changes were generally favourable but were very small and none was significantly different from zero.

DISCUSSION

Pig testing and recording schemes have been operated in many countries for many years, mainly with the object of providing records to assist breeders in their selection of breeding stock. Large amounts of data with details of the performance and pedigree of the test animals have accumulated and these have been analysed frequently by animal geneticists. These analyses have dealt mainly with the estimation of heritabilities and correlations among traits. The genetic parameters so obtained have been the basis for predicting direct and correlated changes by selecting and for designing efficient breeding and testing schemes. Rather surprisingly, however, the simple and more direct methods of genetically analysing the data, used for example by Lush (1936), have rarely been employed. There have been very few attempts to evaluate the effectiveness of the breeding schemes by measuring the amount of selection done on the test results and its effect on the subsequent progeny. Such analyses could be done to advantage on many of the sets of accumulated pig testing data, both to check on the genetic parameters derived from other analyses and to measure the effectiveness of the testing schemes in making genetic improvement.

The advent of progeny testing brought some important changes in pig breeding practice in Great Britain. The testing placed emphasis on test performance rather than on pedigree or on body conformation, and thus sought to identify the requirements of commercial producers and to define these as aims for the pedigree breeders. Indeed an important function of the progeny testing stations in the early years may have been in influencing the goals of the breeders towards the improvement of economically important and heritable traits. The other important function of the testing stations was to provide, for the first time, comparative tests under standard conditions so that breeders could assess the merit of different stocks in making their selections. Thus progeny testing at once provided both the aims and a means for improvement.

The testing was well supported by the breeders but only a small amount of selection was done on the basis of test results. The selection differentials for the four traits examined here were only about 0·05 to 0·30 standard deviation units which represents a rather mild degree of selection. Several factors may have contributed to the lack of selection, among them a conservatism among the breeders, a lack of advice and guidance on the use of the test results, uncertainty on breeding objectives and some confusion wrought by differences in performance at different stations. However, possibly the most important limitation to selection and improvement was the small number of boars tested relative to the number of sires required in the testing

herds. Although about 250 boars were tested per year there were some 300 herds testing from 1958 to 1962 and some 700 herds in all were eligible for testing. Thus the simple logistics of testing were unfavourable so that few breeders could test regularly and the scope for selection was quite limited.

The usefulness of the progeny test in practice for discriminating among parents in their breeding value was confirmed by the parent-offspring regressions. These were all positive and were generally in line with theoretical estimates. To this extent the regressions found here support the estimates of genetic parameters from other analyses and indicate that the parameters will be fairly reliable in practice. This is reassuring because one cause of concern has been that an effect of pre-test herd environment on the test results may exist. The results given here on this topic are inconclusive, especially as they apply to spans of up to 5 years in herd environment. Studies with Danish pigs showed that from 0 to 6% of the total variation within years could be due to a pre-test herd environment effect (Jonsson and King, 1962; Jonsson, 1963). Although these percentages were rather small, they could, if real, bias heritability estimates quite seriously. It might be noted here that if genetic differences between herds exist, then at least two heritability estimates could be appropriate, one referring to variation within herds and the other to the variation in the whole testing population.

The main conclusion from this analysis is that progeny testing so far has had little impact on pig improvement in Great Britain. Little selection has been done on the basis of test results perhaps partly because only a small fraction of herd sires could be progeny tested. Rather than vastly increasing testing facilities to serve the large national breeding population, an alternative would be to restrict the testing to a small nucleus set of breeders. These breeders could concentrate on testing and selection and would form a nucleus for improvement which would then pass on improved breeding stock to the rest of the population. Such a scheme has been shown to be theoretically the most efficient in the use of a set of testing facilities (Smith, 1959).

This analysis has also shown that the genetic parameters previously estimated are fairly reliable in practice and so can be used with some confidence in designing testing systems and recommending breeding plans. The two chief objectives in pig improvement in Great Britain at present, feed efficiency and carcass lean percentage, are highly heritable and can be measured directly or indirectly on the live animal. In this situation the maximum rate of improvement will obtain from performance testing (Dickerson and Hazel, 1944). The advantages which the performance test can confer in the intensity of selection possible, in the range of performance available for selection and in allowing a low generation interval, cumulatively far outweigh any small loss in accuracy in assessing the breeding value of individual animals. At the current stage of pig improvement in Great Britain, breeding methods more sophisticated than performance testing with mass selection would not appear to be necessary or worthwhile.

SUMMARY

From 1958 to 1962 over 800 boars and 3,000 sows were progeny tested at the national pig progeny testing stations in Great Britain. Their test results for four traits (daily gain, feed efficiency, average backfat and carcass

length) have been used to study the amount and effectiveness of selection and to review the use of the test facilities and their effect on pig improvement.

The amount of selection on test results was studied by measuring the difference in performance of animals with sons subsequently tested and all contemporary tested animals. The selection differentials found were from 0·05 to 0·30 standard deviation units for the four traits studied which represents a rather mild degree of selection. Thus selection could have had only a small effect in improving the testing population. In fact sons of tested animals showed little advantage over their contemporaries in test performance. Parent-offspring regressions were calculated and these, in agreement with theoretical estimates, indicated that selection would be effective and would lead to genetic changes in any of the four traits studied. Genetic correlations among the four traits were also calculated and indicated genetic compatability in improving the four traits concurrently.

Two proposals intended to increase the impact of testing on pig improvement are put forward. These are (1) to restrict the testing facilities to a small nucleus set of breeders who could concentrate on testing and selection and (2) to replace the progeny testing by performance testing which would allow a more intense selection and a greater rate of improvement for the same testing facilities.

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A NOTE ON THE HERITABILITY OF MUSCLE COLOUR IN PIGS

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MUSCLE colour has been recorded on pigs tested at the national pig progeny testing stations in Great Britain since 1958. From September 1960 a muscle colour score on a scale of 1 to 7 points has been given by comparing the muscle colour with a series of seven coloured discs of increasing colour intensity. These discs were prepared specifically (by Tintometer Ltd. of Great Britain) to score muscle colour in pigs. The higher the colour score the more desirable the colour was adjudged to be by the testing station personnel. However, scores of 6 and 7 were very infrequent and no assessment of their desirability was made. Carcasses were cut at the last rib on the day after slaughter at about 200 lb. live-weight and muscle colour was scored on the cut surface of the *longissimus dorsi* muscle (eye muscle).

Data on muscle colour scores were available on the progeny of some 100 Landrace and 149 Large White sires, all with 4 litters of 4 pigs (2 females and 2 castrated males) tested during the period 1960 to 1963. Sires and their progeny were classified into three groups of approximately equal size to reduce the effects of any trends either in muscle colour or in the way it was scored. The grouping was according to the date of start of the progeny test and there was thus some overlapping in the slaughter dates of pigs in different period groups. A conventional nested analysis of variance was performed separately for each sex, and also for the two sexes together. The analyses were within groups and within stations. Heritability estimates were calculated from the components of variance in the usual way (e.g. Smith, King and Gilbert 1962).

The average muscle colour scores for the two breeds and sexes are given in Table 1. The Landrace breed had a lower average colour score than the

TABLE 1

Average muscle colour scores and standard deviations for two breeds and sexes

		Muscle colour score	Standard deviation
Landrace	Castrated males	3·59	0·77
	Females	3·67	0·84
Large White	Castrated males	3·91	0·74
	Females	4·06	0·77

Large White breed and castrated males had lighter coloured muscles than females. In Danish pigs, Jonsson (1963) did not find any difference in muscle

colour score between the two sexes, except in one year when the females had significantly lighter coloured muscles. There were no marked seasonal differences in the present data, but Jonsson (1963) found that the muscles of Danish pigs were darker coloured in winter than in summer.

The proportions of the total variation in muscle colour score attributable to different causes are given in Table 2. The heritability estimates were larger

TABLE 2

Proportions of the total variation in muscle colour score attributable to different causes

		Additive genetic variation (heritability)	Litter variation	Residual variation
Landrace	Castrated males	0·41±0·12	−0·02	0·61
	Females	0·55±0·12	−0·22	0·67
Large White	Castrated males	0·34±0·11	−0·02	0·68
	Females	0·17±0·10	0·10	0·73

in the Landrace breed which had the lower average score and the larger total variation. Jonsson (1963) in two separate analyses, found rather different estimates of heritability in the two sexes, namely 0·06 in castrated males and 0·32 in females, but this pattern was not repeated in the present British data. Estimates of the proportion of the variation due to common litter environment were rather variable in this analysis, but Jonsson (1963) found low positive estimates in Danish pigs.

It was possible in this analysis, to test for sex by litter interaction and sex by sire interaction effects by combining the within-sex analyses and the overall analysis. It turned out that none of the interaction effects was significant in the two breeds.

It is concluded that muscle colour in pigs, as measured by the scoring system used at the British testing stations, is moderately heritable and that selection for muscle colour would result in a genetic change in the average muscle colour score.

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GENETIC PARAMETERS OF BRITISH LANDRACE BACON PIGS

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THIS paper presents the results of an analysis similar to that reported by Smith, King and Gilbert (1962) on Large White pigs. The heritabilities of 26 traits and the phenotypic and genetic correlations among the traits have been estimated from data on Landrace pigs tested at the five British pig progeny testing stations and the results are compared with estimates from previous analyses. The importance of sire-sex and litter-sex interactions was also studied for the 26 traits. Finally a summary of the interrelationships among the traits was attempted using a principal component analysis.

MATERIAL AND METHODS

The form of the data involved and the methods of analysis used were essentially similar to those in Smith *et al.* (1962). Individual performance records were obtained on 574 Landrace litter groups, each of 2 females and 2 castrated males, giving a total of 2,296 pigs by 250 boars tested at the British pig progeny testing stations between 1959 and 1961 inclusive. The numbers of boars with 1, 2, 3, 4, 5 and 8 litter groups were 67, 94, 43, 43, 2 and 1 respectively.

In the analysis of Large Whites constants were fitted for stations and periods but here, to avoid any effects due to changes in the ranking of the 5 stations in different periods, the analysis was made within stations. Separate analyses were performed for each sex and adjustment was made to the data for the effects of eleven 3-monthly periods using dummy variates, i.e. the sums of squares and cross products (S.S.P.) of each trait were corrected for differences due to periods by multiple regression. Adjustments for effects of differences in age at start of test and in last live-weight were also made by multiple regression. The adjusted S.S.P. within stations were then pooled and the components of variation estimated for each sex separately and then together.

To find the S.S.P. for the sire-sex and litter-sex interaction terms, the same form of analysis was performed on the litter totals. By subtracting the S.S.P. for litter totals from the pooled within-sex S.S.P., the interaction S.S.P. in the analysis of variance were found and their significance tested. The interaction effects were also expressed as genetic correlations between performance in the two sexes following Robertson (1959).

The relationships among parents, required for an interpretation of the variance components, were obtained from a sample of 85 Landrace sires tested. The average genetic relationships between a sire and his mates and among the mates of a sire were 0·021 and 0·082 respectively. The degrees of freedom, the expected mean squares and the composition of the components of variance were:

	Degrees of freedom	Expected mean squares	Composition of variance components
Between sires	245	$\sigma_1^2+2\sigma_2^2+4{\cdot}586\sigma_3^2$	$\sigma_3^2 = 0{\cdot}281\sigma_G^2$
Between litters within sires	274	$\sigma_1^2+2\sigma_2^2$	$\sigma_2^2 = 0{\cdot}230\sigma_G^2+\sigma_L^2$
Within litters	564	σ_1^2	$\sigma_1^2 = 0{\cdot}489\sigma_G^2+\sigma_E^2$

where σ_G^2, σ_L^2 and σ_E^2 refer to the additive genetic, non-genetic litter and residual variances respectively and have the same interpretation as in Smith *et al.* (1962).

Twenty-six traits were studied in this analysis of which 21 were also included in the analysis of Large Whites. These will not be redefined here but can be seen, for example, in Table 1. The other traits were:

Average backfat thickness—(shoulder+loin 2)/2.

Carcass depth—maximum depth from the sternum to the top of the vertebral column.

Scores assessing the suitability of the carcass for bacon measured on a scale of 0–50 with intervals of 5 points—(*a*) firmness of fat score, (*b*) eye muscle score and (*c*) fat distribution score.

These 26 traits were chosen from some 40 traits available as representing four broad arbitrary biological categories shown by the grouping in Table 1. These were (1) growth rate, feed efficiency, appetite and dressing out percentage, (2) measures of fatness, (3) carcass dimensions and (4) measures of muscling.

RESULTS

The mean performance and standard deviation for each of the 26 traits are given in Table 1. Differences between the sexes were very similar to those found previously in Large Whites.

Heritability estimates were calculated separately for each sex but the estimates differed significantly ($P<0{\cdot}05$) only in the case of feed intake per day at 200 lb. live-weight. However, the standard errors of the differences were about 0·18 so that discrimination between the estimates in the two sexes was not very powerful. The pooled heritability estimates (standard errors about 0·10), the proportions of the total variation due to non-genetic litter effects (standard errors about 0·04) and the residual proportions of the variation are given in Table 1. For comparison the heritability estimates from the analysis of Large Whites are also tabulated. The estimates in the two breeds differed significantly ($P<0{\cdot}05$) in only two traits, fat depth K and feed intake per day at 125 lb. live-weight, and the agreement between the estimates in the two analyses was quite good. Measures of fat depth and carcass dimensions again showed high heritabilities while the measures

Parameters for 26 traits: means, within sex standard deviations (S.D.), proportions of the variance attributed to different causes, the genetic correlation between performance in the two sexes and the vectors and latent roots of the first two principal components (I and II) of the genetic correlation matrix

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Traits		Mean	S.D.	Additive genetic variance (Heritability)	Litter variance	Residual variance	Heritability Large White †	Genetic correlation between sexes ‡	Vectors I	Vectors II
Daily gain (lb./day)	1	1·45	0·11	0·41	0·11	0·49	0·41	0·66**	−0·12	−0·17
Feed efficiency (lb. feed/lb. carcass gain)	2	4·34	0·26	0·48	0·05	0·46	0·58	0·96	0·25	−0·02
Feed per day at 50 lb. live-weight	3	2·31	0·22	0·19	0·16	0·64	0·26	>1·00	−0·04	0·09
Feed per day at 125 lb. live-weight	4	5·47	0·35	0·15	0·18	0·66	0·66	>1·00	0·15	−0·03
Feed per day at 200 lb. live-weight	5	7·18	0·43	0·41	0·04	0·55	0·34	0·92	0·09	−0·24
Dressing-out percentage	6	74·2	1·60	0·26	0·09	0·65	0·40	>1·00	−0·08	0·47
Average backfat (mm.)	7	32·5	3·30	0·74	−0·02	0·28	0·66	0·81**	0·26	0·07
Flare weight (lb.)	8	5·16	1·19	0·50	0·05	0·45	0·61	0·92	0·21	0·15
Fat depth C (mm.)	9	22·5	3·76	0·62	0·04	0·33	0·65	0·92	0·29	0·21
Fat depth K (mm.)	10	25·5	4·00	0·42	0·08	0·50	0·73	0·95	0·28	0·21
Streak E (mm.)	11	9·70	1·66	0·36	0·12	0·51	0·29	0·81	0·14	0·23
Firmness of fat score	12	38·7	3·43	0·41	−0·08	0·66	—	0·69*	0·14	−0·00
Fat distribution score	13	34·7	5·34	0·29	0·06	0·65	—	0·86	−0·28	−0·14
Carcass length (1st rib) (mm.)	14	811·7	19·5	0·87	−0·04	0·17	0·60	0·91*	−0·10	−0·24
Loin length (mm.)	15	370·5	15·2	0·39	0·02	0·59	0·46	0·70*	−0·12	−0·32
Leg length (mm.)	16	596·1	15·1	0·46	0·14	0·41	0·50	0·79*	−0·10	−0·24
Carcass depth (mm.)	17	257·4	11·1	0·56	−0·01	0·45	0·34	0·56**	−0·06	0·02
Head weight (lb.)	18	17·7	0·99	0·29	0·18	0·53	0·49	>1·00	−0·09	0·01
Fillet weight (lb.)	19	18·4	2·20	0·54	0·00	0·45	0·31	>1·00	−0·17	0·22
Eye muscle A (mm.)	20	79·9	4·73	0·65	−0·01	0·35	0·46	0·34**	−0·23	0·16
Eye muscle B (mm.)	21	48·5	3·95	0·38	0·02	0·60	0·48	>1·00	−0·20	0·24
Eye muscle area (sq. cm.)	22	27·8	2·88	0·49	0·06	0·46	0·35	0·79*	−0·25	0·26
Streak D (mm.)	23	23·3	3·40	0·22	0·03	0·75	0·24	0·69	−0·05	0·15
Back rasher score	24	33·6	7·67	0·34	0·10	0·56	0·59	0·79	−0·34	−0·03
Eye muscle score	25	37·3	4·65	0·41	0·04	0·54	—	0·82	−0·31	0·16
Ham score	26	34·1	5·22	0·22	0·12	0·65	0·35	0·70	−0·22	0·16
Latent root									7·88	4·09

† Smith *et al.* (1962). ‡ *P<0·05, **P<0·01.

of muscling had rather larger heritability estimates in this analysis than in the analysis of Large Whites. The estimates for daily gain and feed efficiency were in good agreement in the two analyses, confirming, as noted in Smith *et al.* (1962), the substantially higher heritability of these traits with individual feeding than was obtained by other authors with pigs on group feeding.

In the analysis of variance to test for interactions of parent and sex of offspring none of the litter-sex interaction terms was significant. The S.S.P. of litter-sex and of within sex and litters were pooled to test for sire-sex interaction effects. The expected variance ratios (F-test values for 245 and 1403 degrees of freedom were found using a formula in Lindley and Miller (1953). Nine of the 26 traits studied (see column 7 of Table 1) had significant ($P<0{\cdot}05$) sire-sex interaction terms. Four of these were traits of high economic value and four were traits associated with carcass dimensions. However, though the sire-sex interactions were significant for these traits, their interaction components accounted for only about 4% of the total variation in the combined analysis.

Robertson (1959) has shown how two effects contribute to an interaction component and these, in terms of a sex-sire interaction are (1) differences in the sire components in the two sexes and (2) differences in ranking among sires for performance in their male and female progeny. The latter effect can be represented by the genetic correlation between performance in the two sexes and these are shown in Table 1 for the 26 traits. Since the interaction term involves the sire components, the test for sex-sire interaction is more sensitive and the standard errors of the genetic correlations are smaller for the traits with high heritability. Only the traits with significant interactions had genetic correlations significantly different from unity, and *vice versa*, so that it appears that the interaction effects were largely due to a different ranking among sires in their male and female progeny performance.

Phenotypic and genetic correlations were estimated for each sex and were subsequently pooled over sex. The pooled estimates are presented in Table 2, the standard errors of the phenotypic and genetic estimates being around 0·02 and 0·18 respectively. To provide a simple measure of the agreement among any two sets of correlation estimates, the correlation coefficient between the corresponding items in the two sets of estimates may be used. This was felt to be a reasonable criterion here for the estimates in any set were fairly normally distributed. The agreement between the sets of estimates in the two sexes was closer for the phenotypic correlations ($r = 0{\cdot}96$) than for the genetic correlations ($r = 0{\cdot}61$) as might be expected from the larger standard errors of the latter. The pooled genetic correlations were similar to the pooled phenotypic correlations ($r = 0{\cdot}86$) but tended to be somewhat larger. This suggests that in the absence of reliable estimates of genetic correlations, it may be expedient to estimate them from the phenotypic correlations. The overall agreement between the pooled genetic correlations calculated both in this analysis and in the analysis of Large Whites was satisfactory ($r = 0{\cdot}62$) though there were several individual differences in the relationships among the traits.

The general impression of the 650 correlations in Table 2 is one of a complex and intricate set of relationships among the traits which is hard to summarise. Among the measures of fatness and fat depth and among the measures of muscling, the traits were fairly highly correlated while

TABLE 2

TABLE 2

Phenotypic correlations (above the diagonal) and genetic correlations (below the diagonal) among 26 traits

	Daily gain	Feed efficiency	Feed per day at 50 lb.	Feed per day at 125 lb.	Feed per day at 200 lb.	Dressing-out percentage	Average backfat	Flare weight	Fat depth C	Fat depth K	Streak E	Firmness of fat score	Fat distribution score	Carcass length	Loin length	Leg length	Carcass depth	Head weight	Fillet weight	Eye muscle A	Eye muscle B	Eye muscle area	Streak D	Back rasher score	Eye muscle score	Ham score
Daily gain		−·67	·09	·30	·40	−·30	−·08	−·24	−·11	−·06	−·12	·04	·08	·13	−·05	−·08	−·26	−·07	−·01	−·09	·03	−·04	−·18	·06	−·01	·07
Feed efficiency	−·71		·04	·16	·06	−·08	·22	·33	·28	·25	·17	·04	−·16	−·05	·05	−·07	·09	−·12	−·23	−·17	−·24	−·25	·11	−·30	−·26	−·20
Feed per day at 50 lb.	·21	−·03		·08	·06	·02	·03	·04	·03	·04	−·02	·03	−·02	·00	·00	−·05	−·01	−·04	−·03	−·04	·00	−·01	−·01	−·01	−·03	·04
Feed per day at 125 lb.	·21	·36	·13		·42	−·02	·18	·14	·24	·26	·10	·07	−·12	·06	−·03	−·17	−·11	−·18	−·15	−·18	−·11	−·19	·07	−·25	−·20	−·06
Feed per day at 200 lb.	·50	·24	·03	·69		·17	·16	·05	·16	·21	·02	·07	−·08	·08	−·02	−·18	−·19	−·14	−·16	−·29	−·15	−·24	−·04	−·23	−·24	−·06
Dressing-out percentage	−·38	−·15	·20	−·48	−·57		·14	·21	·18	·15	·20	·02	−·12	−·12	−·03	·02	·22	·07	·19	·23	·23	·25	·29	−·07	·19	·16
Average backfat	−·26	·44	−·07	·21	·08	·08		·28	·53	·56	·28	·15	−·47	−·19	−·06	−·31	−·13	−·13	−·23	−·29	−·12	−·25	·10	−·36	−·30	−·16
Flare weight	−·25	·45	·07	·52	−·01	·12	·40		·40	·37	·11	·12	−·21	−·12	·02	−·19	−·03	−·21	−·13	−·19	−·12	−·19	·15	−·23	−·23	−·15
Fat depth C	−·44	·48	−·02	−·03	·01	·19	·63	·49		·81	·40	·19	−·37	−·22	−·16	−·24	−·12	−·19	−·25	−·34	−·29	−·38	·15	−·72	−·46	−·20
Fat depth K	−·25	·42	·10	·29	·05	·16	·61	·57	·94		·41	·20	−·36	−·20	−·17	−·31	−·15	−·21	−·24	−·35	−·20	−·33	·14	−·75	−·41	−·14
Streak E	−·27	·20	−·11	−·13	−·10	·25	·33	·15	·56	·67		·05	−·20	−·12	−·09	−·09	−·05	−·07	−·11	−·11	−·06	−·14	·29	−·34	−·19	−·05
Firmness of fat score	−·02	·28	−·01	·29	·23	·08	·31	·24	·40	·56	·00		−·07	·02	·06	−·07	−·04	−·08	−·08	−·07	−·10	−·11	·01	−·17	−·10	−·08
Fat distribution score	·31	−·50	·20	−·48	−·07	−·08	−·80	−·34	−·68	−·55	−·40	−·17		·21	·10	·19	·03	·09	·14	·18	·09	·17	−·11	·38	·16	·20
Carcass length	·21	−·12	−·07	−·25	·19	−·34	−·22	−·19	−·37	−·39	−·18	·20	·32		·28	·20	−·24	·07	−·05	−·07	−·03	−·09	−·16	·18	−·02	−·06
Loin length	·02	·04	−·09	−·28	−·03	−·66	−·04	−·17	−·61	−·56	−·56	·17	·67	·42		·19	·03	·05	−·03	−·03	−·09	−·09	·02	·06	−·03	−·14
Leg length	·22	−·23	·09	−·26	·12	−·36	−·29	−·76	−·29	−·12	−·06	·08	·58	·39	·21		·21	·20	·05	·14	−·06	·03	−·11	·24	·07	−·19
Carcass depth	·00	−·10	·00	·04	−·22	·08	−·31	−·07	−·09	−·16	−·06	−·08	·12	−·27	·13	·28		·02	·11	·24	·00	·13	·09	·11	·14	−·02
Head weight	−·12	−·22	·31	−·74	−·12	·06	−·01	−·32	−·34	−·36	−·07	−·22	−·23	−·19	·11	·10	−·11		·04	·01	·01	−·02	−·16	·19	·04	−·11
Fillet weight	·10	−·51	·28	−·38	−·25	·63	−·32	−·02	−·23	−·19	−·08	·02	·08	·01	−·13	−·12	·15	·36		·27	·25	·31	·03	·28	·30	·15
Eye muscle A	·10	−·38	−·09	−·23	−·29	·39	−·31	−·28	−·41	−·34	−·13	−·03	·45	·03	−·02	·03	·15	·16	·28		·25	·63	·08	·44	·62	·27
Eye muscle B	·13	−·39	·17	·03	−·29	·42	−·28	−·19	−·30	−·16	−·13	−·14	·24	·07	−·11	·04	−·08	·05	·48	·47		·68	·03	·38	·65	·31
Eye muscle area	·14	−·46	·19	−·03	−·24	·57	−·36	−·23	−·33	−·22	−·06	−·17	·48	−·05	−·13	·02	·06	·21	·40	·80	·79		·05	·50	·76	·33
Streak D	−·07	·19	·76	·40	·18	·35	−·04	−·05	−·01	·03	·00	·14	·21	−·07	·16	−·20	·33	−·12	−·01	·10	·28	·34		−·12	·02	·11
Back rasher score	·24	−·58	·05	−·53	−·20	·17	−·62	−·66	−·90	−·84	−·46	−·52	·56	·34	·42	·05	·04	·37	·38	·57	·49	·59	·04		·60	·23
Eye muscle score	·18	−·54	−·06	−·03	−·37	·50	−·53	−·40	−·60	−·55	−·16	−·16	·68	·17	·14	·13	·08	·03	·42	·75	·75	·94	·42	·86		·31
Ham score	·20	−·51	−·02	−·07	−·13	·58	−·53	−·22	−·33	−·14	−·08	−·42	·52	·08	·19	−·20	·03	−·33	·39	·35	·49	·56	·34	·59	·57	

the group of traits measuring carcass dimensions were less closely inter-correlated. The measures of muscling and the various fat depths were inter-correlated but not as highly as might be expected, and neither set of measures were very closely correlated with the carcass length and depth measurements. Of the group of traits representing growth and food intake and utilisation, the most important economically is feed efficiency. The correlations of this with measures of fatness and measures of muscling were larger in this analysis than in the Large Whites indicating that favourable changes in these three groups of traits are quite compatible. Finally, as in the Large White analysis, dressing-out percentage showed positive correlations with both the measures of fatness and the measures of muscling.

Principal component analysis

A principal component analysis was used, as in the analysis of Large Whites, in an attempt to summarise the information in the correlation matrices. The object of such an analysis is to try to explain the correlation pattern among the 26 traits in terms of a smaller number of derived variates, called components, which are linear functions of the original variates. The first component is chosen to account for as much of the correlation pattern as possible, the goodness of fit being assessed by the size of the latent root. Second, third and further components, uncorrelated to those preceding, are chosen in turn, working with the residual correlation matrix at each stage. If the first few components can explain the correlation pattern adequately, it may be sufficient to concentrate on these and neglect the remainder.

While the sum of the latent roots in each case is 26, the number of traits involved, the first two latent roots add up to 12·0, 7·3 and 8·5 for the genetic, environmental and phenotypic correlation matrices respectively. This shows that the first two components can explain a disproportionate part of the correlation matrices especially for the genetic correlation matrix, perhaps because of the higher values of the genetic correlations. In this case the correlations between predicted and observed genetic correlations were 0·54 using the first component and 0·89 using two components. Thus an appreciable description of the correlation pattern was achieved by the first two components.

The vectors of the first and second components were quite similar in the various matrices, though those for the genetic and environmental matrices resembled those for the phenotypic matrix more than each other. This indicates, rather surprisingly, that the main genetic and environmental relationships among these traits were similar but the agreement is likely to be only a function of the groups of fatness and muscling traits used here and not a general biological phenomenon.

The first two latent roots and vectors for the pooled genetic correlation matrix are given in the final columns of Table 1. The first component had high positive vectors for measures of fat depth and feed efficiency and high negative vectors for measures of muscling. Thus, as in the analysis of Large Whites, the predominant relationship among this array of traits is one involving carcass composition and contrasting the measures of fatness with the measures of muscling. The second component had a high positive vector for dressing-out percentage with smaller positive vectors for both the measures of fatness and the measures of muscling and negative vectors for

carcass dimensions and daily gain. The vectors of the third and subsequent components were also studied but it was difficult to find meaningful relationships among traits with vectors of common sign.

A diagram (Figure 1) of the vectors of the first two components was drawn, as in the analysis of Large Whites, for the genetic correlation matrix. It shows that the first two components were able to group related traits

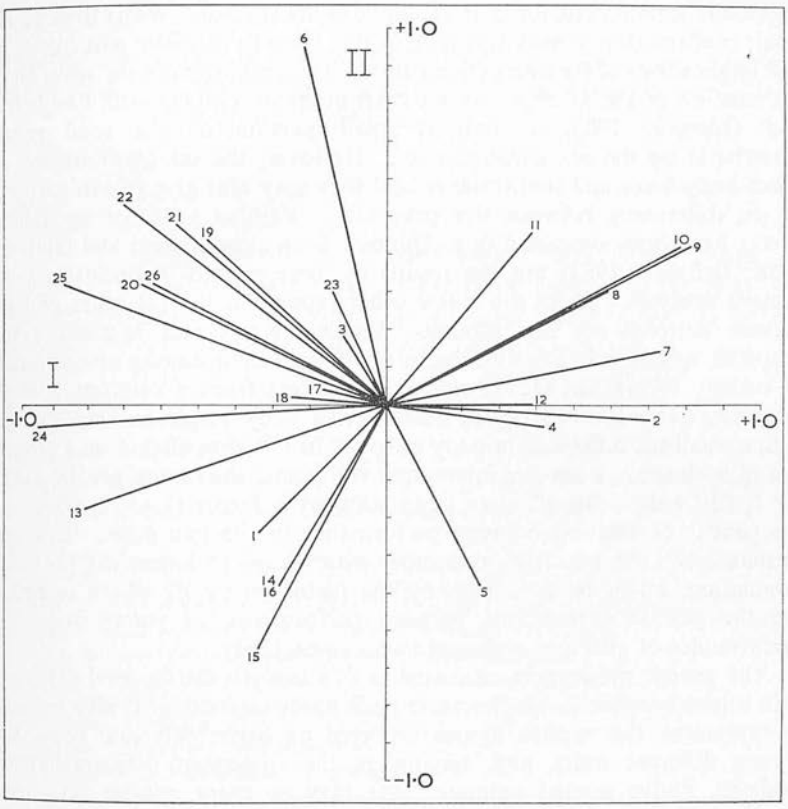

FIG. 1. Diagram of the vectors of the first two components (I and II) of the genetic correlation matrix. (Numbers on the vectors refer to traits listed in Table 1.)

into a common quadrant. Thus the measures of fatness all appear in the first quadrant while directly opposite are two carcass scores, back rasher score and fat distribution score, which are essentially negative measures of fatness. The measures of muscling are more closely grouped here than in the analysis of Large Whites and were again lying at an obtuse angle to, rather than directly opposite the measures of fatness, showing that there is a degree of independence between the two groups of traits. The three skeletal length measurements lay close together in the third quadrant while feed efficiency and two measures of appetite were in the fourth quadrant. Thus the arbitrary classification of the 26 traits into four biological groups (as in Tables 1 and 2) was supported to some extent by the results of the principal component analysis. But rather than representing four independent groups of traits, in which case each group would be identified with a different

component, the array of traits could be represented by two components. This indicates that the relationships among traits in the different groups were more important than their independence.

DISCUSSION

Perhaps the most interesting finding in this analysis was the evidence of sex-sire interactions for nine of the 26 traits studied. While these results await confirmation, it may be useful at this stage to consider possible causes and implications of the interaction effects. The sex chromosome pair is one of the smallest of the 19 chromosome pairs in the pig (McConnell, Fechheimer and Gilmore, 1963) so only a small portion of the total genetic material is on the sex chromosomes. However, the sex chromosomes do affect body form and performance and they may also give rise to variation in sex differences between sire progenies. Various tests for sex linkage effects have been suggested (e.g. Thomas, Blow, Cockerham and Glazener, 1958; Beilharz, 1963) but the results of these proved inconclusive in the present analysis. There are a few other reports in the literature of interactions between sex and strains. Shaklee, Knox and Marsden (1951) reported variation in sex differences for body weight among several strains of turkey. Korkman (1957) was able to select from a common stock of mice one line with a large sex difference in body weight and another line with a small sex difference in body weight. In selection of sires on a progeny test of both sexes, a sex-sire interaction will hinder the rate of genetic change for it will reduce the effective heritability by a factor $(1+r)/2$, where r is the genetic correlation between performance in the two sexes. In a performance test the effective heritability with regard to improving the whole population, might be even less, by the factor $(r_1+r_2)/2$ where r_1 and r_2 are the genetic correlations between performance of young boars and performance of gilts and castrated males respectively.

The genetic parameters estimated in this analysis are in good agreement with others reported in the literature from many countries. It may be useful to summarise the various figures reported on heritability and correlation among different traits, and, relying on the agreement between different analyses, derive pooled estimates that may be more reliable than those obtained in any one analysis. The averages of parameter estimates for nine traits commonly studied were calculated using estimates drawn where available from eight analyses of pig progeny testing data, and these are given together with their sources in Table 3. The measurements and scores representing the different traits were not always identical in the different analyses; for example feed efficiency was calculated either on a live-weight or a dead-weight basis, carcass length was measured to the atlas or to the first rib, carcass backfat was taken as the average of different sets of measurements in different analyses and the scores given for carcass conformation and ham were allocated in different ways though aimed at similar if not identical ideals. These differences in the traits used might be expected to lead to less agreement between the estimates of heritability and correlation in the different analyses. To assess the agreement between the individual estimates averaged in each cell of Table 3, the intra-cell correlation was calculated for each group of parameters. The intra-cell correlation of heritability estimates was only 0·30 due perhaps to the small range in the

average heritabilities for the nine traits. On the other hand, the intra-cell correlations for the phenotypic and genetic correlation groups were 0·82 and 0·69 respectively. The average genetic correlations were again slightly larger than the average phenotypic correlations, but the correlation between the two sets (0·96) was very high. This could be taken to indicate that any anomalies between the genetic and phenotypic correlations in individual

TABLE 3

Average parameters for 9 traits from 8 studies †: heritabilities on the diagonal, phenotypic correlations above the diagonal, genetic correlations below the diagonal

		Traits								
Traits		1	2	3	4	5	6	7	8	9
ly gain	1	0·42§	−0·73	−0·17	0·07	−0·07	0·13	−0·13	0·10	−0·03
d efficiency	2	−0·76	0·48§	−0·05	−0·04	+0·19	−0·17	+0·16	−0·17	−0·16
sing-out %	3	−0·19	+0·01	0·32	−0·19	+0·19	−0·06‡	+0·29	+0·22	+0·15
ass length	4	0·14	−0·08	−0·40	0·62	−0·22	+0·37	−0·14	−0·19	−0·05
fat thickness	5	−0·15	0·21	0·28	−0·30	0·54	−0·34	+0·13	−0·12	−0·13
ass conformation	6	0·28	−0·30	0·00‡	0·46	−0·52	0·28	−0·17	+0·36‡	+0·24‡
thickness	7	−0·03	0·10	0·25	−0·17	0·22	−0·13‡	0·38	+0·07	−0·07
score	8	0·14	−0·24	0·34	−0·23	−0·26	0·37‡	0·19	0·36	+0·27
muscle area	9	−0·11	−0·34	0·36	−0·08	−0·28	0·35‡	−0·16	0·44	0·42

† Fredeen (1953). Canadian Yorkshire, 644 sires.
Fredeen and Jonsson (1957). Danish Landrace, 468 sires.
Johansson and Korkman (1950). Swedish Landrace, 1,693 sires.
Jonsson and King (1962). Danish Landrace, 935 sires.
Jonsson (1963). Danish Landrace, 3,000-4,000 sires.
Osterhoff (1956). Swedish Landrace, 640 sires.
Smith, King and Gilbert (1962). British Large White, 200 sires.
Smith and Ross (here). British Landrace, 250 sires.
‡ Average of only two estimates.
§ Omitting 3 estimates from group fed pigs.

analyses were due to sampling errors in estimation. Thus the average relationship found in several analyses may be treated with more confidence than estimates from only one analysis.

The high average values for the heritability of backfat thickness and carcass length in Table 3 are well known and have been reported in many analyses. Since the genetic and phenotypic correlations are so similar they can be treated together. There are few high correlations in the table but, on the other hand all the traits are inter-correlated with one another to some extent and none can be treated independently. That is, changes in one trait will bring an array of small correlated changes in other traits. Considering the concurrent improvement of the traits studied here, the main set of relationships are favourable and will augment the selection effect. Moreover, when there are incompatibilities they are slight and not binding, and may be overcome, at least initially, in selection. There is some incompatibility in improving dressing-out percentage on the one hand and increasing daily gain or carcass length and reducing backfat thickness on the other.

Another difficulty may be the negative correlation between carcass leng and ham score. Finally, if increasing belly thickness is important, there a small incompatibilities with several other traits.

The agreement among parameter estimates in different analyses reassuring and shows that the distribution of variation in the various testi populations is similar and that the analytical procedures are consiste and robust in extracting relevant portions of the variation. However, must always be borne in mind that the accuracy and value of these par meters in the prediction of genetic change through selection can only assessed by actual breeding and selection work (e.g. Hetzer, Harvey a Peters, 1963).

How useful has the principal component analysis been in these studi of the genetic parameters? As a statistical procedure it has led to a remar able condensation of the information in the correlation matrices of traits, so that a large portion of the information could be expressed by few components and their vectors. In every case the first component cou be clearly identified with measures of fatness on the one hand and wi measures of muscling on the other. However, second and subsequ components, derived from the residual correlation matrices at each sta have been more difficult to interpret and seemed sensitive to changes in t array of traits and to variations in the relationships among them. T difficulty in interpretation is that if the component is not repeatable or h no reasonable biological meaning, it may be unacceptable to the biolog though it may stimulate him to consider the novel association of tra presented. Some simplification of the matrices of correlations could b obtained by manually grouping traits according to their relationships a this may facilitate a general description. However, such a grouping wou be arbitrary while the principal analysis provides a unique solution f each matrix and gives an estimate of the goodness of fit obtained. O the other hand, if a simple manual grouping of the traits could not b achieved then it is unlikely that a principal component analysis would le to a simple solution either. Thus while the latter may provide a use and measurable summarisation of a correlation matrix, by accounting f the main relationships among groups of traits, it is an aid to, rather tha a substitute for, the thorough examination of the correlation matrix and the array of individual relationships among traits.

SUMMARY

Genetic parameters were estimated among 26 traits in British Landra bacon pigs. The data involved 2,296 pigs from 250 boars tested at the fi British national pig progeny testing stations from 1959 to 1961 inclusi Separate analyses were performed for each sex and for the litter tot adjustments being made to the data for differences among periods with stations and for differences in age at start of test and in weight at slaught The genetic parameters were estimated from the sire components in conventional hierarchical analysis of variance.

Estimates of heritability and genetic and phenotypic correlations amo the 26 traits are presented and discussed. The parameter estimates we in very good agreement with figures obtained in a previous analysis w Large White pigs. They indicate that a large part of the variation a

covariation among the 26 traits is genetic in origin, and the traits involved would change in response to selection. Moreover, with regard to their concurrent improvement there were no serious antagonisms in the genetic relationships among the traits studied. There was however, evidence of an interaction of sire and sex of progeny for nine of the 26 traits.

A principal component analysis was used in an attempt to summarise the correlations among the 26 traits. The first two components gave a reasonable fit to the correlation pattern and these were associated with fat depth, measures of muscling and dressing-out percentage.

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A NOTE ON THE HERITABILITY OF LEG WEAKNESS SCORES IN PIGS

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DURING 1963, pigs tested at the five pig progeny testing stations in Britain were examined and scored by each station manager for leg weakness at the end of test. Some 19 individual items were scored, the score being 0 if satisfactory, 1 if a mild fault and 2 if a serious fault. In addition an overall legs and action score was given, scoring on a scale from 1 to 6 points; in this case the higher the score the better the leg condition. Data were available on 1,240 Landrace and 1,892 Large White pigs (2 females and 2 castrated males per litter) from 128 and 202 sires respectively. Sex differences in incidence were small, most of them being less than a tenth of a standard deviation unit, and so the analyses were performed ignoring sex. To avoid any effects of differences in incidence and in scoring among stations and to avoid the effects of any trends in the scoring pattern over the year, the analyses were performed within three-monthly periods within stations.

The scoring of the leg weakness faults was necessarily coarse and arbitrary and it was appreciated that the scale and the incidence of the scores might affect the heritability estimates obtained. Several forms of analysis were used to tackle the problem from different aspects. Conventional half-sib heritability analyses were done on three scales (I) 0/1/2, (II) (0, 1)/2 and (III) 0/(1, 2), treating the leg scores as ordinary variables. The linear scale for the three classes, satisfactory, mild and serious, which would have the maximum heritability, was found for each item by a latent root analysis of the matrix $P^{-1}G$, i.e. the product of the inverse of the phenotypic variance-covariance matrix (P) and the genetic variance-covariance matrix (G) (A. F. Purser, personal communication). Another estimate calculated, using scale (III), was the 'linear' heritability proposed by Abplanalp (1961). Finally, the heritability of liability to leg weakness score (Falconer, 1965) was estimated on scale (III) from the incidence in half-sibs of affected animals. This estimate is independent of average incidence in the population but assumes liability follows a normal distribution.

The average scores for 13 of the items scored are given in the Table. Another seven items with average scores of less than 0·10 were not analysed. The Large White breed scored better for the overall legs and action score than the Landrace breed but it was not consistently better on all individual items. Several items showed significant differences in average score between the breeds and these may reflect breed characteristics in leg weakness.

The half-sib heritability estimates (h^2_S) were quite similar for all three simple scales used. Some increase in the heritability estimates was obtained through using the best linear scales, but the average increase was small (+0·07) and came largely from making negative estimates positive. Moreover, the linear scales obtained were not always meaningful biologically for the serious faults were often scored less than the mild faults or even given opposite sign. The 'linear' heritability estimates (Abplanalp, 1961) were

TABLE

Averages, standard deviations and heritabilities, h_s^2 and h_L^2 (with standard errors) for 13 leg weakness scores

Item		Average score	Standard deviation	Heritability (h_s^2)	Heritability (h_L^2) of liability
	Scale	0/1/2		0/1/2	0/(1, 2)
Hind legs					
Hind legs twisting	L †	0·63 *	0·68	0·32±0·15 ‡	0·12±0·18 §
	LW	0·22	0·47	0·21±0·10	0·23±0·17
Hocks close together	L	0·42 *	0·60	0·09±0·13	0·07±0·15
	LW	0·89	0·69	0·17±0·12	−0·16±0·11
Sickle hocks	L	0·65 *	0·68	0·24±0·14	0·22±0·13
	LW	0·36	0·56	0·03±0·11	−0·03±0·23
Leg turned in	L	0·21 *	0·53	0·56±0·13	0·38±0·19
	LW	0·09	0·32	−0·16±0·16	−0·01±0·07
Leg turned out	L	0·77 *	0·67	0·45±0·16	0·09±0·16
	LW	0·87	0·69	0·27±0·13	0·02±0·15
Clays uneven	L	0·65	0·61	0·29±0·11	−0·12±0·13
	LW	0·66	0·61	0·20±0·11	0·38±0·20
Fore legs					
Knock-kneed	L	0·23 *	0·42	−0·09±0·12	−0·18±0·12
	LW	0·32	0·47	0·09±0·12	0·11±0·21
Over at knee	L	0·19	0·44	0·00±0·11	0·07±0·24
	LW	0·21	0·46	0·00±0·13	−0·19±0·22
Legs turned out	L	0·50 *	0·57	−0·03±0·12	0·19±0·15
	LW	0·69	0·64	0·22±0·11	−0·02±0·17
Legs turned in	L	0·22 *	0·47	0·07±0·09	0·05±0·14
	LW	0·07	0·27	0·21±0·08	0·25±0·15
Down at pasterns	L	0·29	0·55	−0·14±0·16	−0·25±0·17
	LW	0·26	0·50	0·05±0·13	0·06±0·14
Clays uneven	L	0·52	0·56	0·23±0·13	−0·02±0·11
	LW	0·55	0·56	0·18±0·10	−0·14±0·11
	Scale	1 to 6		1 to 6	
Overall legs and action score	L	3·28 *	1·05	−0·02±0·14	
	LW	3·43	1·02	+0·10±0·12	

† L, Landrace. LW, Large White.
‡ Theoretical estimates.
§ Empirical estimates.

* Significant difference (P = 0·05) between breeds.

quite similar to the estimates of heritability of liability (h_L^2), both being functions of the proportions affected in the population and among half-sibs of affected animals.

The h_S^2 estimates on scale (I), and the h_L^2 estimates on scale (III) are given with their standard errors in the Table. For the overall legs and action score the estimated h_S^2 was low in both breeds. This suggests that any general predisposition to leg weakness is rather weakly inherited. For the other 12 items, the h_S^2 estimates on scale (I), and also those on scales (II) and (III) tended to be higher than the h_L^2 estimates. The reverse might have been expected, for, on an all-or-none scale, such as scale (II) or (III), the h_S^2 estimate is theoretically a fraction, $z^2/p(1-p)$, of the h_L^2 estimate, p being the proportion affected and z the ordinate for p in the normal curve (Robertson and Lerner, 1949). The h_L^2 estimates were not correlated with the mean scores while the h_S^2 estimates were. This would be expected over the range of p among the scores, given that the h_L^2 estimates were not correlated with the mean scores. Within each breed the h_L^2 estimates were correlated with the h_S^2 estimates on scale (I) ($r = 0{\cdot}5$), but were even more closely correlated ($r = 0{\cdot}7$) when adjustment was made for differences in mean score, the adjusted heritability estimate being $p(1-p)/z^2$ times the h_S^2 estimate on scale (II). This shows that the various estimates agreed reasonably well about the relative order of the heritability of the various scores within each breed calculated from the same set of data. However, the agreement between the various estimates in the two breeds was very poor, both with and without adjustment of the h_S^2 estimates for differences in mean score. This result contrasts sharply with the good agreement that has been found previously for heritability estimates in the two breeds for a large number of quantitative traits (Smith and Ross, 1965). It may be that the leg weakness scores in fact represent rather different traits in the two breeds. Alternatively the heritability estimates found may be merely sampling results, characteristic of a particular set of data. A general conclusion may, however, be safely drawn from the estimates, namely that the heritability of these leg weakness scores is rather low. Of all the heritability estimates in the Table only eight were significantly different ($P = 0{\cdot}05$) from zero, and in no case was the average of the four estimates of heritability for any one item greater than 0·25.

Two other results may be mentioned. Maternal and litter environment effects, as assessed from the components in the half-sib analyses, were found to be unimportant in affecting the leg weakness scores. The relationship of the overall legs and action score and eight economically important production traits was examined. All the correlations obtained were quite low, none being larger than $\pm 0{\cdot}07$.

Leg weakness is an important source of loss in practice, especially in breeding stock, and further study of its hereditary nature should be worthwhile. It may well be that controlled experiments, using sound and defective parents, would be more useful than data analysis in investigating the problem. However, the results presented here show that the heritability of leg weakness scores is rather low and it would seem that a genetic decrease in the amount of leg weakness in pigs would be slow and difficult to achieve.

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A NOTE ON THE IMPROVEMENT OF A TRAIT BY SELECTING ON ITS COMPONENTS

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MANY traits in farm animals, such as litter size or fleece weight, are the product or ratio of two or more component items. This note seeks to determine the circumstances in which selection directed at the component items is more effective in improvement than selection for the composite trait itself.

A change of one per cent in a product trait can be achieved by a change of one per cent in any of its components. The response expected on selection for a product trait or a component is proportional to h^2C per cent, where h^2 is the heritability and C is the coefficient of variation. Thus selection for a component trait (A) may possibly be more efficient than direct selection for the product trait (X) when $h^2_A C_A$ is greater than $h^2_X C_X$. However, the correlated changes in other component traits would also have to be taken into account.

Rather than select on only one component, ignoring the others, there is likely to be an optimum weighting for each component in selection. If the product trait (X)and components (A, B, . . .) are transformed to a logarithmic scale, the effects of the component traits will be additive rather than multiplicative. That is if

$$X = A \times B \times \ldots \text{ and } G_X = G_A \times G_B \times \ldots$$

then $\log X = \log A + \log B + \ldots$ and $\log G_X = \log G_A + \log G_B + \ldots$

where the G's refer to the genotypic values for the various traits. A selection index can now be derived, using the transformed variates, so as to give the optimum weighting in selection to the various component items. The various phenotypic and genetic parameters would have to be re-estimated on a logarithmic scale. However, functions of the original parameters should be satisfactory as a first approximation, taking $V \log X \doteq C^2_X$ and $V \log G_X \doteq C^2_X h^2_X$. [More accurately $V \log X = C^2_X(1+2{\cdot}75\ C^2_X+9C^4_X+ \ldots)$. The term $VG_{\log X}$ which appears in the heritability of $\log X$, is taken as equal to the term $V \log G_X$ which comes into the index calculations.] This procedure is the same as partitioning V_X and VG_X into terms in A and B, and deriving the index $I = \bar{B}b_1\ (A) + \bar{A}b_2\ (B)$ where $G = \bar{B}(G_A) + \bar{A}(G_B)$, $\bar{A}$ and $\bar{B}$ are the means of the component traits and b_1 and b_2 are index coefficients.

The relative response to different forms of selection can now be expressed and compared for the simple case of a trait (X) the product ($A.B$) of two component traits.

1. Selection of one component ($\log A$) provides a relative response of $(1+gCH)$.

2. Selection on the unweighted sum of the components ($\log A + \log B$)—corresponding to direct selection for the product trait—gives a relative response of $(1+2gCH+C^2H^2)/\sqrt{1+2rC+C^2}$.

3. Selection on an optimum index of the components ($b_1 \log A + b_2 \log$ gives a relative response of

$$(1+gCH)\sqrt{1+\left(\frac{H(g+CH)}{1+gCH}-r\right)^2/(1-r^2)}$$

where $C = C_B/C_A$, $H^2 = h_B^2/h_A^2$ and r and g are the phenotypic and gene correlations respectively.

TABLE 1

Efficiency of selection for a product trait (A.B) on an index (I) and on component (A) relative to direct selection

H^2†	C†	Correlation ($r=g$)‡									
		0·75		0·25		0		−0·25		−0·75	
		I	A	I	A	I	A	I	A	I	A
1·0	5·0	100	82	100	42	100	20	100	5	100	4
	2·0	100	88	100	61	100	45	100	25	100	3
	1·0	100	94	100	79	100	71	100	61	100	5
	0·5	100	97	100	92	100	89	100	87	100	8
	0·2	100	99	100	98	100	98	100	98	100	9
0·5	5·0	113	112	103	66	102	38	100	5	104	8
	2·0	114	114	106	89	105	75	105	56	104	1
	1·0	113	112	106	100	105	94	106	88	109	7
	0·5	110	108	103	102	102	99	102	96	100	8
	0·2	108	104	101	101	100	100	100	99	103	9
0·2	5·0	177	166	130	117	120	85	111	44	117	11
	2·0	166	150	135	133	134	124	136	115	177	10
	1·0	151	134	125	124	120	118	118	111	115	8
	0·5	137	119	111	111	107	106	104	101	101	8
	0·2	126	108	104	104	101	101	100	98	110	9
0·0	5·0	>200	>200	>200	>200	>200	>200	>200	>200	>200	>20
	2·0	>200	>200	>200	>200	>200	>200	>200	>200	>200	14
	1·0	>200	187	163	158	141	141	126	122	107	7
	0·5	>200	141	126	122	112	112	103	100	107	7
	0·2	176	116	111	107	102	102	100	97	130	8

† $H^2 = h_B^2/h_A^2$, ratio of heritabilities,
$C = C_B/C_A$, ratio of coefficients of variation.
‡ r = phenotypic correlation, g = genetic correlation.

Algebraically these expressions are rather complex and so the relati responses were evaluated empirically for a range in values of C, H^2, r and The efficiency of (3) relative to (2) is symmetric for values of CH^2 and $1/CH$ as would be expected since A and B are assigned arbitrarily. Thus in Table results are shown only for $H^2 \leqslant 1$ so that selection in (1) is for the trait w the higher heritability, the case of most interest.

Weighting the components in an index (3) is generally more effici than direct selection (2) for the product trait itself. However, the ge may only be worthwhile when the component traits differ markedly in t heritability, that is when the ratio H^2 is less than 0·5 or greater than

In these cases, however, selecting on the component with the higher heritability may be almost as efficient as selecting on the index. The gains in efficiency tend to be larger when the ratio of the coefficients of variation is inverse to the ratio of heritabilities. When the component traits are strongly correlated the gains through the index tend to be greater, rather more so when the traits are positively correlated than when they are negatively (unfavourably) correlated. This was an unexpected but consistent result. The effects of differences in the genetic and phenotypic correlations on the relative efficiencies were often substantial but showed no consistent pattern.

The rate of improvement in traits with three or more components would also be increased by applying the selection index method. However, the gains in efficiency may be expected to be less than shown here since the circumstances giving worthwhile gains are less likely to occur if several traits are involved.

TABLE 2

Parameters of fleece weight and its components

		Fleece weight W	Surface area S	Wrinkling score R	Fibres per unit area N	Fibre area A	Fibre length L
Coefficient of variation	(C)	0·14	0·07	0·07	0·20	0·16	0·11
Heritability	(h^2)	0·50	0·40	0·35	0·50	0·35	0·45
Correlations $(r=g)$	S			−0·1	−0·1	0·1	0·1
	R				0	0·1	−0·2
	N					−0 6	0
	A						0

The improvement of a linear function involving product traits can also be treated in a similar fashion. For example, if $Y = AB + C$ and $G_Y = a_1(G_{AB}) + a_2(G_C)$, where a_1 and a_2 are the respective economic weights, G_Y can be expanded into $\bar{B}a_1(G_A) + \bar{A}a_1(G_B) + a_2(G_C)$. The selection index then becomes, $I = \bar{B}b_1'(A) + \bar{A}b_2'(B) + b_3'(C)$, and the coefficients can be found in the usual manner.

In practice the advantage from selecting on components may be less than estimated. The gains in efficiency will have to offset the extra effort spent on measuring several components rather than only the trait itself. The index procedure maximises the response for a given set of parameter estimates, each with sampling errors. Thus it may well overestimate the true response compared with the estimates from direct selection which rely on fewer parameters without maximisation. If the traits are normally distributed they will be somewhat skewed on a logarithmic scale and this may affect the selection differentials.

The improvement of fleece weight, a trait that can be represented as the product of five component traits (Turner, 1958), is considered as an example. The parameters available (Table 2) are rather tentative being the averages from various reports. Several of the traits have rather high coefficients of variation which may affect the approximation of their variances on the logarithmic scale. Dealing with heritabilities and correlations is equivalent to standardising the variables. On a standardised logarithmic scale the relative values of changes in the component traits are proportional to the

coefficients of variation. These values then correspond to the econo weights in conventional selection indices.

The selection index for the component traits, each on a standardi logarithmic scale, is $2{\cdot}8S+2{\cdot}5R+9{\cdot}8N+6{\cdot}4A+4{\cdot}9L$ the coefficients be proportional to Ch^2 as expected. The expected response in fleece we through the index is only about two per cent greater than with di selection. Selection on one component would be less efficient than di selection, for example by using (N) alone the efficiency is only 60%. T selection on one component or on a weighted combination of compon traits would not appear to be worthwhile in the improvement of fleece wei

In general it has been shown that selection directed at the component a product trait may well increase the rate of genetic improvement. Howe the procedure may only be worthwhile in special situations, such as w there are marked differences in the heritability and in the variation of traits concerned, and when the traits are highly correlated.

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IMPROVEMENT OF METRIC TRAITS THROUGH SPECIFIC GENETIC LOCI

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IN the past little use has been made of individual genetic loci in the improvement of metric traits in farm livestock. Early workers in animal breeding had found that most metric traits were not inherited in a simple Mendelian manner, and had sought other methods of improvement. More recently evidence has been presented (e.g. Briles, 1961; Ashton, 1960) that certain identified loci may affect metric traits in farm animals and interest in individual loci has been revived. Much current research effort in animal genetics is being spent in detecting simple Mendelian loci, especially blood group factors and serum protein polymorphisms. Two uses of this research will be to provide an efficient means of parentage testing and to study the dynamics of many simple genetic systems in farm animal populations. Of more immediate interest to animal breeders are the effects that individual loci may have on metric traits, and the possibility that selection through 'known' loci may prove an efficient means of genetic improvement. (The term 'known' loci refers to any identified loci for which individuals can be typed.)

Additive genetic variance

The usefulness of known loci in selection will depend on the amount and on the accuracy of the information they provide about an animal's breeding value for the metric trait concerned. These can be expressed in the context of quantitative genetics and the factors determining their usefulness may be determined.

A formal description of phenotypic effects, breeding values and variances at a locus is necessary. This is given in Table 1, following Falconer (1960), for the case of two alleles assuming random mating.

TABLE 1

Breeding values and variances at one locus (assuming random mating)

	Class			Variance
Genotype	A_1A_1	A_1A_2	A_2A_2	
Frequency	p^2	$2pq$	q^2	
Average merit†	a	d	$-a$	
Genotypic value‡	$(a-m)$	$(d-m)$	$-(a+m)$	$2pq\alpha^2+(2pqd)^2$
Breeding value	$2q\alpha$	$(q-p)\alpha$	$-2p\alpha$	$2pq\alpha^2$

Class	A_1-	A_2A_2	
Class frequency	p'	q'	
Average merit	D	0	
Genotypic value	$(D-m)$	$-m$	$D^2p'q'$
Breeding value§	$2q^2\alpha/(1+q)$	$-2p\alpha$	$4pq^2\alpha^2/(1+q)$

† Expressed as deviations from the mean of the homozygous groups.
‡ $\alpha = a+d(q-p)$, m = overall mean.
§ Estimable only if a and d are known.

The breeding value of each phenotypic class is twice the deviation of its expected progeny mean from the mean of progeny of all classes (Table 1). When several independent loci affect a trait, the aggregate breeding value of an individual is simply the sum of the breeding values at these loci. The variance in breeding value (Table 1) is also the additive genetic variance in the trait at that locus.

In practice the parameters, shown in Table 1, are not known but must be estimated from performance data on the average merit of each phenotype. The estimates of breeding value are unbiased but are subject to sampling errors. This causes the variance in breeding value to overestimate the additive genetic variance available for selection. The bias is removed by subtracting the term $2pqV(\hat{\alpha})$, where $V(\hat{\alpha})$—the variance of the estimate of (α) (Table 1)—is $\sigma^2/2pqN$, (N) being the number of animals tested and (σ^2) the variance of the trait involved. The unbiased estimate of the additive genetic variance available for selection is thus $2pq\hat{\alpha}^2-\sigma^2/N$. For (m) independent known loci this becomes $\sum_m 2p_m q_m \hat{\alpha}^2 - m\sigma^2/N$, the sum of their individual contributions. The ratio of this quantity to the total additive genetic variance (VG) for the trait is given the symbol (R). This ratio (R) is used throughout the rest of the paper as measure of the value of known loci in selection and improvement.

The estimates of (R), obtained in practice from sets of data, will have sampling errors. The variance of (R) can be shown, following Neimann Sørensen and Robertson (1961), to be

$$\frac{2}{Nh^2}\left[2R+\frac{m}{Nh^2}\right]$$

Later it is shown how this variance is relevant in assessing the value of known loci in improvement.

More complex forms of phenotype arrays can now be considered. When only two phenotypic classes are detected at a locus (Table 1), the additive genetic variance controlled is less by the factor $2q/(1+q)$ than if the three genotypes were each identified. Many of the loci that have been detected in farm animals have multiple alleles. The greatest ultimate improvement through these loci will come, if the effects are additive, from fixing the allele with the largest effect (overdominant effects are considered later). Increasing the frequency of other favourable alleles in the interim may increase the immediate rate of improvement, but at the expense of later improvement because more selection effort will then have to be spent in eliminating these other alleles. Thus, for improvement of a trait, multiple alleles can be conveniently grouped into two classes: (1) the allele (or alleles) with the largest effect and (2) the others. This makes the case for multiple alleles the same as that for two alleles (Table 1). Linkage between loci has no effect on the additive genetic variance when the loci are in linkage equilibrium (Cockerham, 1956).

Overdominant loci $(d > a)$ contribute to the additive genetic variance (Table 1) until they reach equilibrium frequency. The full response from an overdominant locus can only be got by developing two separate breeding lines (say 1 and 2), each homozygous for a different allele (for multiple alleles take the two alleles giving the best heterozygote). On crossing the lines, all the progeny are then heterozygous at the locus. The estimated breeding values of the three genotypes in line (1), measured on their crossline progeny with line

(2) are $2q_1\hat{\alpha}_2$, $(q_1-p_1)\hat{\alpha}_2$ and $-2p_1\hat{\alpha}_2$, where the subscripts now refer to the two lines. The variance in estimated breeding value in line (1), measured on crossline progeny, is $2p_1q_1\hat{\alpha}_2^2$ and this includes variation from both additive and overdominant loci. Adding over (m) loci and adjusting for the bias as before, the additive genetic variance available for selection at these loci then becomes $\sum_m 2p_{1m}q_{1m}\hat{\alpha}_{2m}^2 - m\sigma^2/N$, and similarly for line (2). The ratio of the sum of these two quantities to twice the total additive genetic variance for crossline performance (VG_C) is again designated (R). Thus, selection at overdominant loci can be treated in the same way as selection at additive loci in a single line.

Response to selection

The genetic response expected on selection is of the form

$$\bar{\imath}cb_{GP}\sigma_P,$$

where $(\bar{\imath})$ is the selection differential in standard deviation units, (c) is the reciprocal of the average generation interval and (b_{GP}) is the regression of breeding value (G) for the trait concerned on (P) the criterion used for selection. Responses expected for several possible methods of selection are summarised by the formulae given in Table 2. The efficiency of the various methods of selection can be compared conveniently on this basis.

TABLE 2

Responses expected to different methods of selection

Method of selection	Expected genetic response ($h^2\sigma$ units per period)
(1) On individual performance (mass selection)	$\bar{\imath}_1c_1$†
(2) On known genetic loci	$\bar{\imath}_2c_2\sqrt{R/h^2}$‡
(3) On a selection index of (2) and (1)	$\bar{\imath}_1c_1(1+\frac{1}{2}R/h^2)$§
(4) By two-stage selection, first on (2) then on (1)	$\bar{\imath}_1c_1(1+(\bar{\imath}_4/\bar{\imath}_1)\sqrt{R/h^2})$
(5) By indirect selection on relatives	$\bar{\imath}_5c_5r/w$
(6) On a selection index of (2) and (5)	$(\bar{\imath}_5c_5r/w)(1+\frac{1}{2}(R/h^2)(w^2/r^2))$§

† $\bar{\imath}$—selection differential, c—reciprocal of the generation interval. For family selection multiply by $(1+(n-1)r)/nw$, where w^2 equals $(1+(n-1)t)/n$, the variance of the mean of n tested relatives; t is the correlation among tested relatives and r is the genetic relationship of the selected individual with its tested relatives.

‡ R—the proportion of the additive genetic variance controlled by known loci.

§ Approximately.

From Table 2 it is apparent that the value of known loci in selection depends on the ratio R/h^2, that is on the proportion of the total additive genetic variance controlled by known loci relative to the heritability of the trait concerned (Neimann-Sørensen and Robertson, 1961). This ratio appears in all the formulae where known loci are concerned and the expected responses increase when the ratio increases, that is when (R) rises or the heritability falls.

The responses are also affected by the selection intensity $(\bar{\imath})$ and the generation interval $(1/c)$ which apply to the different forms of selection. In general,

selection on known loci can be made earlier and more intensely than indiv dual or index selection, which in turn will tend to be more intense and at a earlier stage than indirect selection on relatives. These factors must be take into account in comparing different selection methods.

The response to selection on known loci, relative to that by mass selection is $k\sqrt{R/h^2}$, where (k) represents the term in $(\bar{\imath})$ and (c) (here $k = \bar{\imath}_2 c_2/\bar{\imath}_1 c_1$). The relative efficiency, shown graphically in Figure 1, rises as (R) increases but only exceeds unity when (R) is greater than h^2/k^2. For a given value of (R) the response from known loci will be greater as (k) rises and (h^2) falls. However, in the latter case, selection efficiency can be improved by using family selection, thus raising the effective heritability of the trait.

Rather than being considered as alternatives in selection, performance data and information on known loci may be combined usefully in a selection index (Neimann-Sørensen and Robertson, 1961). The gains in efficiency over individual selection are then proportional to R/h^2 and are also shown in Figure 1. At high heritabilities, even if half of the additive genetic variance is due to known loci ($R = \frac{1}{2}$), the efficiency of selection can be raised by only 20–30%. For traits with low heritability, however, useful gains in efficiency can be obtained. For example, when (R) equals h^2, gains in response of 40–50% would be obtained through a selection index.

Selection in two stages, first on known loci and then on performance will be more effective than index selection when

$$(2\bar{\imath}_4/\bar{\imath}_1)^2 > R/h^2$$

This is quite possible if (R) is small relative to (h^2), or if the initial selection is much more intense than the final selection. Thus, this method may be suitable for using loci which affect traits with high heritability and where there is scope for intense early selection.

In the improvement of many economic traits in farm animals, such as sex-limited or carcass traits, indirect selection on sibs' or progeny performance must be used. Since the information on known loci can be obtained for all breeding animals, it is likely to be more useful in this case. The efficiency of selection on known loci relative to indirect selection can also be gauged from Figure 1, using $(k'w/r)^2R$ as the scale for the abscissa. Both (w/r) (*see* Table 2) and (k'), the term in $\bar{\imath}$ and c, are likely to be larger than unity so the gain in efficiency will be greater than with direct selection for a given value of (R). Similarly, in a selection index, information on known loci will add (w/r) times the gain in improvement expected through an index for direct selection.

Information on known loci may also be more useful in traits showing overdominance. Selection on crossline performance requires a progeny test whereas information on known loci is available for the breeding animals and no cross testing is necessary. The gains here from known loci will thus be the same as for indirect selection.

On occasion two lines may be developed merely to exploit a few over-dominant loci with large effects. In this case direct selection for performance may still be possible within lines and any gain in efficiency through known loci may then be less than if indirect selection was used.

Use of individual loci

A simple way to use a locus in improvement is to make the population homozygous for the best allele. This will take only one or two generations

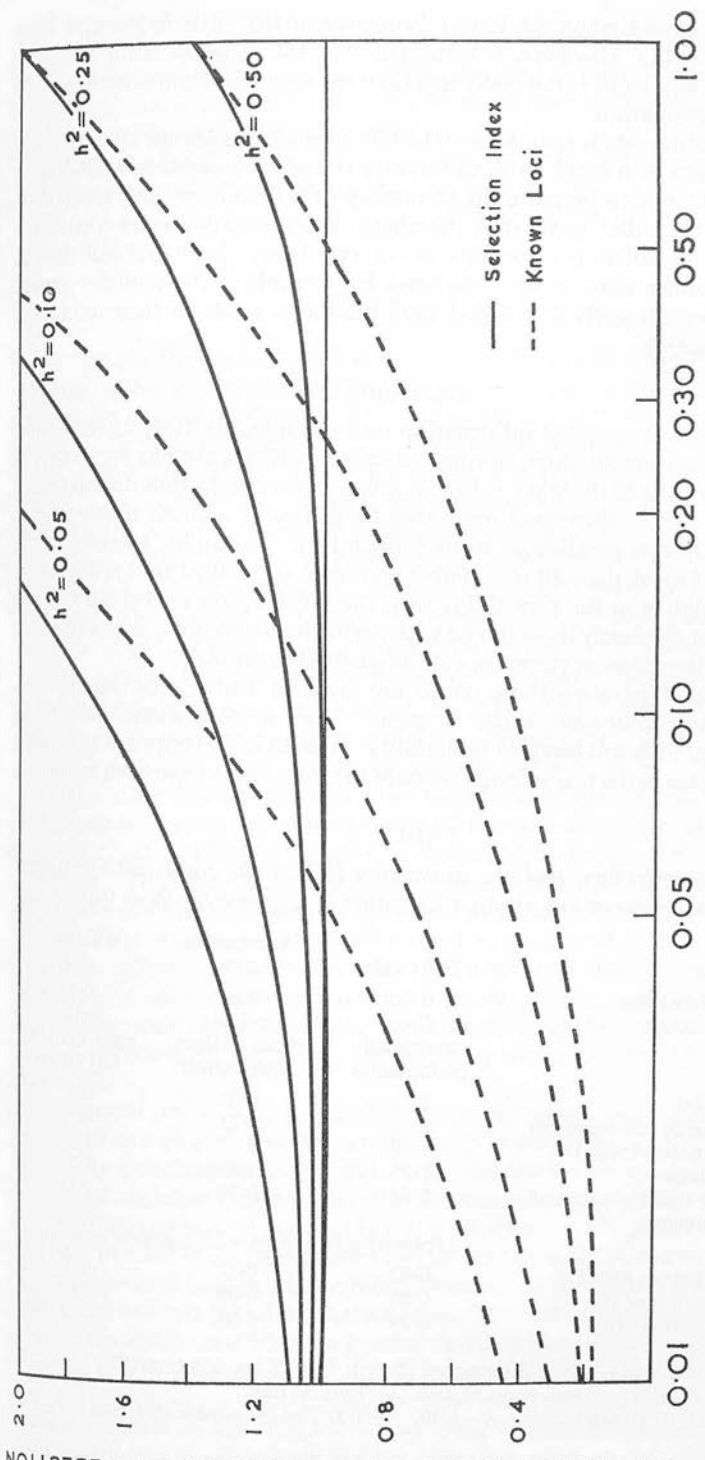

FIG. 1. The efficiency of selection on known loci alone and in a selection index, relative to individual selection.

of selection except when the initial frequency of the allele is low and when selection is mild. However, it turns out that the response from fixing the better allele at a locus is normally less than the response from selecting on all available information.

In two situations it may be worthwhile to make an abrupt change in the gene frequency at a locus so as to increase the genetic variance available for selection. One is to increase the frequency of a favourable but uncommon allele, and the other is to shift the alleles at an overdominant locus from equilibrium in different directions in the two lines. Such loci can then be exploited sooner than would otherwise be possible if the additive genetic variance they currently controlled were used as a guide to their immediate value in selection.

DISCUSSION

It has been shown that information on known loci is likely to be of most value in improvement when normal selection methods are not very effective such as when the heritability is low or when indirect selection on relatives is necessary. Some advantage may also be gained if a more intense or an earlier selection is possible by using known loci. Normally, however, if the proportion (R) of the additive genetic variance controlled by known loci is not large relative to the heritability (h^2), the information on known loci will be used most efficiently if combined with performance records, as in a selection index, and the gains in response can be easily determined.

Examples illustrating these points are given in Table 3 for the improvement of three economic traits in pigs. They involve direct or indirect selection and different levels of heritability. Values of (R) required to provide a 25% increase in the rate of improvement for these traits have been estimated.

TABLE 3

Responses to selection, and the proportion (R) *of the total additive genetic variation due to known loci giving a* 25% *gain in response for three traits in pigs*

	Daily gain	Eye muscle area	Litter size
Heritability	0·4	0·4	0·1
Method of selection	direct	indirect	indirect
Selection on	individual performance	mean of three litter mates†	mean of dam's two litters†
Relationship (r)	1	0·5	0·5
Standard error of test mean (w)	1	0·73	0·76
Generation interval (years)	1	1	1
Selection differential‡	1·7	1·3	1·7
Response per year (in standard deviation units)	0·68	0·38	0·13
	(*Proportion* (R) *giving a* 25% *gain in response*)		
Selection on known loci (2)§	0·62	0·17	0·07
Index selection (3) or (6)	0·20	0·09	0·02
Two stage selection (4)	0·40	0·03	0·05

† Eye muscle area—half of litter tested (2 ♂, 1 ♀), half for selection (1 ♂, 2 ♀). Litter size—2 litter records per dam, progeny selected from 1st litter.

‡ One boar per 10 sows: Select ♂—1/30, ♀—1/3. For eye muscle area, select ♂—1/10, ♀—1/2.

§ Numbers refer to methods of selection listed in Table 2.

The results follow the patterns described above. A certain gain in response can be got with progressively smaller values of (R) by using a selection index, as indirect selection becomes necessary and as the heritability falls. It is apparent that even small values of (R) could provide worthwhile gains in improvement in certain practical situations.

In recommending a method of selection in practice the variance of the response predicted should be taken into account (e.g. Searle, 1966). For selection on known loci this variance will depend on the variance of (R), shown earlier to be

$$\frac{2}{Nh^2}\left[2R+\frac{m}{Nh^2}\right]$$

If the number (m) of loci used is not large, (R) will be proportional to its variance so that Nh^2 must be large to estimate (R) accurately. The responses to selection depend on the ratio R/h^2 and so errors in (R) will be more important if the heritability is low. This is unfortunate because it is for traits with low heritability that information on known loci is most likely to be useful. Errors in estimating (R) will cause the selection effort to be misdirected, by giving undue weight in selection to the information from known loci. When the estimate of the effect of the locus is very inaccurate, less progress could be made than if the locus were not considered. Thus (R) has to be well estimated before it can be used with confidence in formulating breeding plans in practice.

How large a sample of animals should be tested to provide a reliable estimate of (R). Using the criterion that the value of (R) should be more than twice its standard error, (N) equal to $8(1+\sqrt{1+m/8})/Rh^2$ animals, or approximately $20/Rh^2$, would be required. When either of the proportions (R) or (h^2) is small, large samples of animals will have to be tested.

Many other factors may affect the usefulness of known loci in selection. For example, account should be taken of the cost of typing individuals for the useful loci relative to the cost of measuring individual or progeny performance. Normally in farm livestock, several traits will combine to determine the overall performance or economic merit of an individual or breeding group. Thus, it is the *net* effect of known loci on overall performance, rather than their effects on one trait, that will determine their usefulness. It is possible that specific loci may not have similar effects in all lines or breeds, or in all environmental situations. This would limit the value of such loci in general improvement schemes, though they may still be useful in specific situations.

At present, most loci are found through their serological and biochemical properties and only afterwards are their effects on economic traits examined. Thus, any associations found will be by chance rather than design. This process of apparent random detection is unsatisfactory for, even if there are loci with large effects, there is only a low probability of finding them among the large number of loci which are segregating (an exception is for segregating (overdominant?) loci in highly inbred lines). Thus, it may be expected, *a priori*, that any loci found by current procedures will account for only a small proportion of the total additive genetic variance in a trait. Any exception to this rule will be a fortunate but infrequent event. Moreover, if the information on known loci is reliable, selection through them will be accurate, and so the duration of the response may thus be rather short—unless there is a continuous detection of further new loci with useful effects. These

factors suggest that the role of known loci in animal improvement will be opportunistic rather than routine and continuous.

Recently, loci having large effects on quantitative traits were found by using backcrossing schemes in lines already differentiated by trait selection (Spickett and Thoday, 1965; Wehrhahn and Allard, 1965). Finding useful loci in retrospect may be of little value in improvement, but these studies suggest that other metric traits may also be controlled by a few major loci. This would affect the design of breeding plans and the prediction of response to selection (Latter, 1965) and may stimulate a search in farm animals for new loci with large effects.

A large number of loci are now known in farm animals but how useful are they likely to be in livestock improvement? Mitscherlich (1965) cites some 57 known factors (about 12 loci) in chickens, 88 (21 loci) in cattle, 34 (12 loci) in sheep and 57 (20 loci) in pigs, these being mostly blood group antigens and polymorphisms of blood and body fluids. Associations of many of these factors with various economic traits have been reported and a summary of those with the larger effects is given in Table 4 for these four species.

TABLE 4

A summary of the larger reported effects for specific loci on economic traits in farm animals

Trait		Locus	Effect	Standard deviation of trait	Number of animals	Remarks
Chicken						
Livability	(1)	B. (Heterozygotes versus homozygotes)	+6%	—	7,700	Several reports on overdominance
Egg production	(1)		+4%	—	1,400	effects at B locus
Hatchability	(2)	B. ,,	+25%	—	4,000	
Cattle						
Butterfat%	(3)	B. (BO_1Y_1D')	0·064%	0·3%	1,409	Confirmed in two further reports
Milk yield	(4)	*M*	−322 kg.	850 kg.	242	Further reports conflicting
Milk yield	(5)	Tf (*AA–DD*)	−26 gals.	180 gals.	141	Not confirmed in further reports
Fertility	(6)	Tf (Homozygotes versus Heterozygotes)	+7%	—	780	Further reports conflicting
Sheep						
26 traits	(7)	7 Blood groups	—	—	2,507	No consistent effects found (4,877 comparisons made)
Pig						
Carcass length	(8)	/27	+1·8 cm.	2·5 cm.	684	Not confirmed in further reports (1,122 comparisons made)
Daily gain	(8)	Max.	+30 g.	60 g.	684	

(1) Briles and Allen (1961). Within 7 inbred lines.
(2) Morton *et al.* (1965). Within a closed commercial strain.
(3) Neimann-Sørensen and Robertson (1961). Within Red Dane bull progeny groups.
(4) Mitscherlich *et al.* (1961). Within East Friesian bull progeny groups.
(5) Ashton (1960). Among progeny groups of British A.I. bulls.
(6) Ashton (1961). Among cows of the Jersey and of the Shorthorn breeds.
(7) Stanfield *et al.* (1964). Within several breed groups.
(8) Baltzer (1963). Among pigs of the improved German Landrace breed.

There have been several reports showing overdominant effects for fitness traits at the B locus in chickens. These effects may be useful in practice, since fitness traits tend to have low heritabilities and often are sex-limited. For most of the other loci, the effects cited in Table 4 are either unconfirmed or further studies have produced conflicting reports. Thus, from the array of loci known at present in farm animals, none could be used with confidence in livestock improvement schemes.

SUMMARY

Known genetic loci that affect metric traits may be useful in livestock improvement. Their value depends on the proportion (R) of the total additive genetic variation due to the known loci relative to the heritability of the trait concerned and on the form of selection practised. When normal selection is effective, further information on known loci can add only a little to the rate of improvement. But if normal selection is not very effective, as for characters of low heritability, or if indirect selection on relatives must be used (as for sex-limited or carcass traits) then known loci may add significantly to the rate of improvement possible.

Sampling errors in the estimated effects and in the proportion (R) may cause selection effort to be misdirected and may even lead to losses rather than gains in improvement. Such errors are most likely to occur when the heritability of the character is low.

Reports on several loci with large effects in the various farm species have been summarised, but the evidence is often inconsistent and contradictory. At present, there appear to be no loci that could be used with confidence in the improvement of economic traits in farm animals.

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HERD DIFFERENCES AND GENETIC TRENDS IN IOWA PIGS [1]

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SINCE the advent of the central swine testing stations in Iowa, there have been substantial improvements in the performance of pigs measured in the testing stations. This is often taken as evidence on the effectiveness of the testing scheme and is assumed to be due to genetic changes in the breeds. More critical studies on these points are needed. Unfortunately, the data from the testing stations are not suited for a definitive analysis on these topics because genetic and environmental differences between herds and years are confounded with differences among sire progeny groups.

This report concerns three studies of genetic changes and differences among Iowa pigs. The first study was to assess the importance of genetic differences between herds, and the second was to measure the genetic trend in performance by using records on progeny from sows of different ages. The data in these studies were collected in an experimental herd, the boars used in the herd being purchased from breeders involved in the testing program. The third study was to evaluate the policies used in selecting boars for breeding in purebred herds. The data were collected from a questionnaire sent to breeders who had submitted animals to the testing stations.

Material

Data for the first two studies came from a herd used to study the genetic effects of paternal irradiation in pigs. The effects of irradiation on the traits considered here were negligible and will be ignored in this paper although the design used to measure the effects will be utilized. The design of the experiment has been described previously (Willham and Cox, 1962) and only relevant details will be repeated here. The herd was formed in 1959 by purchasing pairs of full brothers and pairs of full sisters from purebred Duroc and Hampshire herds in Iowa. Sows farrowed twice per year, in spring and fall, within two restricted 6-wk. periods. All matings were purebred. Each litter was born and raised in one pen, the male pigs being castrated before they were 3-wk. old.

Every 6-mo. a new set of males, 15 pairs of full brothers per breed, was purchased to sire the pigs in one period. The breeders contacted for boars were individuals submitting test groups to the swine testing station at Ames. Boars were purchased on the basis of competitive bids without reference to herd or individual performance records. The procedure provided a wide sample of breeders who used the testing station. Often two pairs of boars were purchased from one breeder if the pairs were not by the same sire. This allowed a partition of the variance into herd and sire components to evaluate the importance of genetic herd differences.

Replacement females were taken from litters born in the herd by dams in their first or second parity. All females were retained for two litters and then, to maintain herd size, were culled at random irrespective of their reproductive status. Thus, an array of unselected sows of different ages, or parity, was available in each period as shown in table 1. The rows represent the number of litters produced by dams born in any period, and the columns show the number of litters born in any period.

This array made an estimate of the genetic trends in the breeds possible.

Two traits were considered in these studies. One was liveweight gain from 98- to 154-days of age, adjustments (table 2) being made for sex, litter size and weaning weight. The adjustments were derived from a least-squares analysis which included the age of the dam in the model. The adjustments were, therefore, independent of the age of the dam and of the genetic trends with which age of the dam is confounded. The other trait studied was average backfat probe, taken on the live animal at 154 days of age and adjusted for 154-day weight by the regression of the average probe on 154-day weight within breed, litter and sex (table 2).

The data for the third study were obtained from a questionaire sent to breeders asking what criteria they used in their choice of boars for breeding. The questionaire (Appendix) was sent in May, 1967, to 138 pedigree breeders who were currently testing groups in the

[1] Journal Paper No. J-5782 of the Iowa Agricultural and Home Economics Experiment Station, Ames. Project No. 1424. This work has received assistance from Contract AT(11-1)-707 with the U.S. Atomic Energy Commission.

TABLE 1. ARRAY OF LITTERS BY PERIOD OF FARROWING AND PERIOD OF BIRTH OF DAM

Year and period of birth of dam			Year and period of farrowing											
			1961		1962		1963		1964		1965		1966	
			1	2	3	4	5	6	7	8	9	10	11	12
	1960	1	132	77	64	50	42	33	25	22	22	14	12	8
		2	...	141	118	52	49	40	28	27	19	14	9	5
	1961	3	...	...	60	39	36	32	35	22	20	10	11	7
		4	...	...	...	92	84	38	39	32	22	14	13	12
	1962	5	...	...	...	..	52	42	28	27	19	11	13	11
		6	...	...	...	..	..	68	62	37	22	11	11	10
	1963	7	...	...	...	..	..	..	83	68	24	14	12	10
		8	...	...	...	..	..	..	..	57	37	17	15	15
	1964	9	...	...	...	..	..	..	..	..	90	68	61	42
		10	...	...	...	..	..	..	..	..	..	25	23	0
	1965	11	...	...	...	..	..	..	..	..	..	..	86	62
		12	...	...	...	..	..	..	..	..	..	..	..	47

testing station or who had tested recently. Seven breeds were represented. Questions were posed about the age, origin and reasons for choice of the boar being tested and of the youngest boar in the herd. The manager of the testing station designated one-third of the breeders as prominent in their breed. Seventy-one breeders (51%) answered the questionaire.

Methods and Results

Herd Differences. The purchase of two unrelated pairs of boars from each of several herds in the same season allowed an estimate of the importance of genetic herd differences. A nested analysis (table 3) was made of the adjusted records on individual pigs, arranged within periods and within sire-treatment groups (irradiated *vs.* non-irradiated). The treatment classification blocked the data into groups of unrelated males mated to unrelated females since the members of a pair of full brothers were always assigned to opposite treatment groups. Grouping the data by period removed the effects of any genetic trends. Many herds were sampled in several different seasons so that the degrees of freedom for herds were much larger than the total number (84) of herds involved. This introduces no bias in the estimates of the herd components, but would exaggerate their precision.

Differences due to herd of sire must be genetic since the progeny were raised con-

TABLE 2. AVERAGES FOR LIVEWEIGHT GAIN AND BACKFAT PROBE WITH LEAST SQUARES CONSTANTS AND REGRESSIONS USED IN ADJUSTING THE DATA

Item	Duroc		Hampshire	
	Castrated males	Females	Castrated males	Females
Liveweight gain from 98 to 154 days (kg.)	47.2	43.0	41.9	38.0
Regression of gain on litter size (kg./pig)	—0.18	—0.18	—0.13	—0.13
Regression of gain on 42-day wt. (kg./kg.)	0.94	0.94	0.94	0.94
Sex constants for gain (kg.)	2.08	—2.08	1.96	—1.96
Av. 154-day wt. (kg.)	87.2	82.0	79.0	74.4
Av. backfat probe (mm.)	34.9	29.9	27.2	24.3
Regression of probe on 154-day wt.(mm./kg.)	0.398	0.378	0.318	0.308

emporaneously on the same farm and came rom a random mating with a large group of ows. The component of variance for herds n the nested analysis includes any herd by eriod interactions, that is, fluctuations in the erd rankings over time. The percentage of ariation due to herd differences was very mall for both traits in both breds (table 3). hus, no evidence was found for important enetic differences in growth or fatness among erds.

The heritability estimates based on the ariance components for sires within herds for he gain from 98 to 154 days and for backfat robe were about 15% and 40%, respectively, nd similar to estimates in other reports (e.g., raft, 1958). On the other hand, analyses of ire families in data from the testing stations, here family differences were largely conunded with herd differences, have shown very gh estimates of heritability (Sutherland, 58). This suggests that herd effects are not all, and now with little evidence of genetic fferences between herds, it would seem that e herd influence on testing station results largely environmental. This could be due to etest effects and to methods of managing d selecting pigs entering the test.

Genetic Trends. The phenotypic trends gure 1) for gain and for backfat probe were vorable and consistent in boars tested at the sting stations. Little trend was found for her trait measured in the experimental herd. Dams born in different periods were offring of successive groups of sires purchased 6 mo. intervals from perigree breeders. Genetic differences between dams of different ages, therefore, would indicate genetic changes in the breed. In any period all dams were mated at random to a group of sires recently acquired from the breed. Thus, the regression of progeny performance on the age of the dam within a farrowing period measures approximately one-half of the average genetic trend in the breed. A negative regression, occurring if the progeny of older dams had lower values than the progeny of younger dams, would indicate a positive trend in the breed. A positive regression would indicate a negative trend in the breed.

Any effect of age, or parity, of dam is confounded with the estimate of genetic trend. As described in the Materials section, adjustments were made to gain and to backfat probe. These adjustments should remove some of the main effects of the dam's age on the gain and fatness of her progeny, although other effects may still remain confounded with the estimates of genetic trend. Furthermore, adjustment for litter size and weaning weight assumes that there was no genetic trend in these traits. If these traits did change with time and were correlated with gain and fatness, the adjustments would remove a portion of the trend in the later traits.

The regressions within periods of the adjusted litter means on the age of the dam, measured to the nearest half-year, were calculated and then pooled, weighting by the reciprocal of their variance. The estimates of the average genetic trend based on the regressions are given in table 4. The estimates of genetic

TABLE 3. ANALYSIS OF GAIN AND OF ADJUSTED BACKFAT PROBE WITHIN GROUPS OF SIRES TREATED ALIKE AND BORN IN THE SAME SEASON

Source	d.f.	Coefficients in expected mean squares $\sigma^2_P+\sigma^2_D+{}^2\sigma^2_S+\sigma^2_H$				98- to 154-day gain Variance component	%	Adjusted backfat probe Variance component	%
uroc									
Herds	157	1.0	7.8	34.9	47.5	0.08±0.98*	0.1	0.002±0.006	0.7
Sires/herds	83	1.0	7.7	28.5	...	1.94	3.1	0.028	10.0
Dams/sires	983	1.0	6.8	...	...	17.89	28.7	0.062	22.1
Pigs/dams	7463	1.0	...	...	...	42.40	68.0	0.189	67.2
						h^2**=.12±.08		h^2=.41±.12	
ampshire									
Herds	159	1.0	7.3	34.0	46.6	−0.15±0.87	...	0.000±0.004	0.0
Sires/herds	80	1.0	7.3	30.4	46.6	2.19	4.5	0.015	9.3
Dams/sires	1062	1.0	6.4	...	...	15.10	30.9	0.043	26.7
Pigs/dams	7411	1.0	...	...	...	31.56	64.6	0.103	64.0
						h^2=.18±.09		h^2=.38±.11	

* Approximate standard error.
** Heritability $(h^2)=4\sigma^2_S/(\sigma^2_P+\sigma^2_D+\sigma^2_S)$.

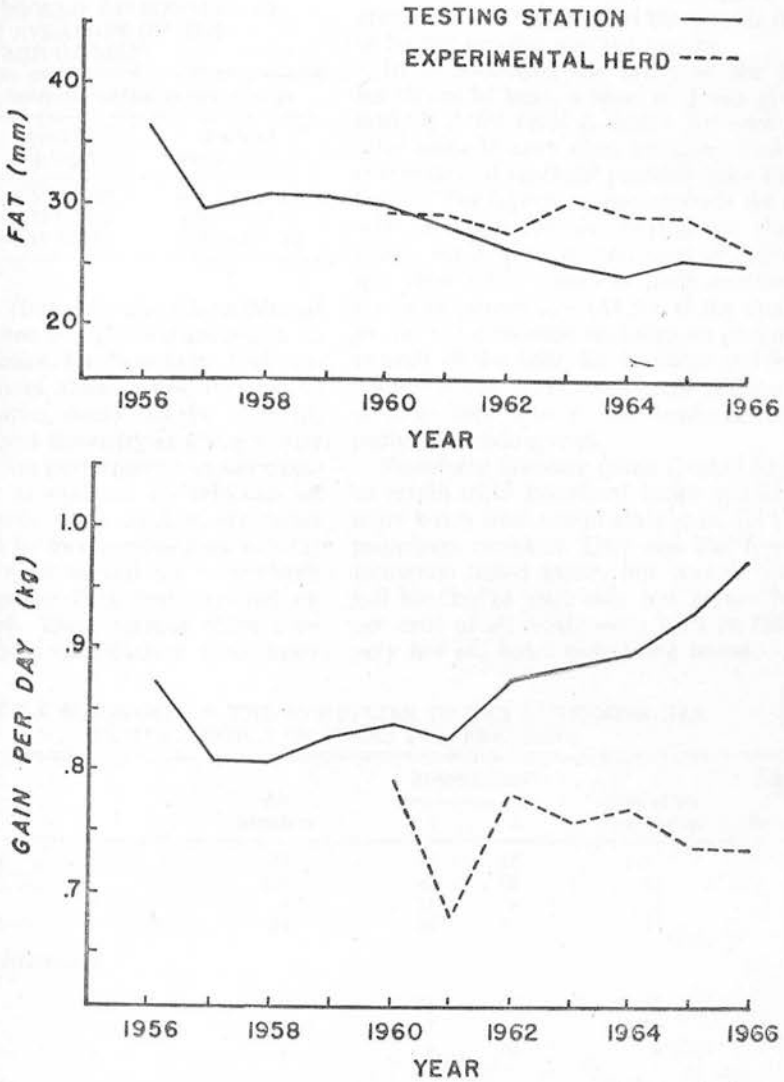

Figure 1. Time trends in yearly averages of gain and backfat for the Iowa Swine Testing Station and the experimental herd. Testing station averages are for boars, experimental herd averages are for barrows and gilts.

change in gain from 98 to 154 days differ in the two breeds, their average trend being small. The estimate of genetic trend in backfat probe was positive in both breeds, younger dams having fatter progeny than older dams. All fat measures were adjusted for 154-day weight. The estimate of the average change was $+0.35 \pm 0.10$ mm. per year, about one-tenth of the standard deviation. The phenotypic trend in backfat probe of the boars measured at the testing station was about -1.0 mm. per year.

Choice of Boars. Over half the breeders replied to the questionnaire. Their replies provide a guide to their reasons for the choice of boars for breeding and are summarized in table 5. Few boars (9%) were bred on the farm where they were used, and none of the herds replying were closed to outside stock. About one-third of the boars were purchased from outside the state of Iowa. Differences in merit among herds or among states seem unlikely to exist or develop with so much exchange of breeding stock.

Some 18% of the boars had been performance tested and a further 10% had sibs that

TABLE 4. GENETIC TRENDS ESTIMATED FROM THE POOLED REGRESSION OF LITTER AVERAGES ON THE AGE OF MAN

tem	Estimated annual genetic change	
	98 to 154 gain (kg.)	Backfat probe (mm.)
uroc	−0.55±0.30	+0.04±0.18
ampshire	+0.55±0.25	+0.49±0.12
ver-all	+0.11±0.19	+0.35±0.10

ad been tested. Thus, only about one-third of he boars had some test performance data to upport their choice for breeding. Unfortuately, the merit of these boars, relative to heir contemporaries, could not be assessed.

A rather different summary is given if any anking (1 to 3) on performance in the quesionaire is taken as evidence for selection on erformance records. Then 31% of the boars sed were ranked for own performance record; further 29% were ranked on a brother's ecord and a further 22% were ranked on heir sire's record. These records often conerned carcass data on relatives from litter certification or meat-sire certification programs. Again, the merit of the records referred to by the breeder was not known.

In summarizing the ranks of the reasons for choice of boar, a score of 3 was given for rank 1, 2 for rank 2, and 1 for rank 3, the total score in each class being expressed as a percentage of the total possible score (6 x 125 boars). The type and appearance of the animal was the most popular reason for choice of boars, while pedigree and herd of origin were less often cited. Together these accounted for the same percentage (45%) of the total score as did the combined rankings on performance records of the boar, his brothers and his sire. Thus, visual assessment and pedigree still seem as important as test results in choice of pedigree breeding stock.

Prominent breeders (class 1, table 2) tended to retain more homebred boars and also buy more boars from out-of-state than did the less prominent breeders. They also had fewer performance tested boars, but several used the full brother of their own test group. Seventy per cent of all boars were born in 1966 and very few old boars were being tested.

TABLE 5. SUMMARY OF THE 70 REPLIES TO THE QUESTIONNAIRE ON THE CHOICE OF BOARS FOR BREEDING

Item	All breeders	Breeder class[a]		Sire of the test group	Youngest sire in the herd
		1	2		
replies	51	55	48	..	..
o. of boars	125	47	78	73	52
homebred	9	17	4	5	13
bred out-of-state	31	38	27	35	25
of boars with a performance test cited					
) On boar	18	13	22	23	9
) On sib[b]	10	17	6	10	12
) On sire[c]	2	4	0	1	2
of boars with any record cited					
) On boar	31	21	37	34	27
) On sib[b]	29	40	22	28	29
) On sire[c]	22	21	23	21	23
easons for selection of boar (Summary of ranks)[d]					
ype and appearance	29	29	29	24	36
oar performance record	13	10	15	15	9
b performance record	15	16	14	15	14
re performance record	18	16	19	17	19
edigree	10	9	11	10	9
erd of origin	5	5	5	6	5
ther[e]	9	14	6	11	7

[a] Classed into prominent (1) and other breeders (2) by the manager of the testing station.
[b] Without a test on the boar.
[c] Without a test on the boar or his sibs.
[d] Rank 1=3 points; 2=2 points; 3=1 point; expressed as percentage to total rank score.
[e] Includes dam record, length, price, availability, bone, muscling appearance, progeny record, feet and legs, wt. for age, show ord, unclassified, etc.

Discussion

These studies indicate that the genetic differences between herds and the genetic trends in the breeds have not been as large as the results at the testing stations would suggest. The high rate of exchange of breeding stock probably accounts for the lack of genetic differences between herds and both belie the genetic superiority usually credited to herds prominent in the breed hierarchy or successful at the testing stations. Jonsson (1965) found that farm environment differences accounted for about 8% of the variation in daily gain and for about 2% of the variation in fatness in pigs tested at the Danish progeny testing stations.

The estimates of genetic change are perhaps the least satisfactory of the results presented because the estimates are confounded with any effects of the age of the dam or parity not removed by the data adjustments. Also, any genetic change in the breed was assumed to be linear and to be transmitted directly to the successive groups of females in the experimental herd. The same purchasing procedure and array of herds was used throughout the experiment. However, the possibility exists that breeders were more selective early in the work and less careful about the boars supplied in later periods. There was no conscious selection among females in the herd and an investigation showed that the average merit of females entering the herd or being culled was the same as that of their contemporaries so that the effects of chance or natural selection could be discounted.

As judged by the questionaire, type and appearance are still very important to breeders in their choice of boars for breeding. Most boars had some records that could be cited to support their choice, but the relative merit of these records and their use in selection are still undetermined. Certainly the results of performance tests do not have priority in the selection of boars and the direct effects of the testing stations on genetic improvement cannot be great. Moreover, no general policy exists whereby the sons of selected boars would be tested and selected in turn so accumulating genetic improvement.

The dilemma is raised, as with the Danish Landrace (Smith, 1963), whether the phenotypic trend from the testing station data or the estimated genetic trend is nearer the true genetic change in the breeds. The trends in backfat thickness for pigs in Iowa and in Denmark are compared in table 6 with the responses obtained in two selection experiments (Gray *et al.*, 1965; Hetzer *et al.*, 1963). The experiments were small but selection was solely for low backfat measured by a live probe at about 80 kg. liveweight. Selection differentials of 0.7 to 0.9 standard deviation units per year were achieved and realized heritabilities were high. Breed improvement involves many traits of which backfat thickness is an important item. However, in this study and in the Danish work (Smith, 1963), there seemed to be little direct selection against backfat thickness based on the test results. Yet the changes per year in backfat thickness of the two breeds were similar to those in the experiments, and on a generation basis the former were twice as large. Such a result was not expected because it would appear more difficult to change a breed, with its multiple objectives and large number of breeders, than to change a small line selected for a single trait. Is it possible that the large number of breeders involved, their wide choice of breeding stock from many herds and states, their intimate knowledge of individual animals and

TABLE 6. TRENDS IN BACKFAT THICKNESS OF PIGS IN IOWA AND IN DENMARK AND IN TWO EXPERIMENTAL HERDS

Location	Iowa	Denmark	Beltsville	Missouri
Breed	Duroc and Hampshire	Danish Landrace	Duroc and Yorkshire	Poland China
Objective	Breed improvement	Breed improvement	Selection on backfat probe	Selection on backfat probe
Period (yr.)	10	12	11	5
Generation interval (yr.)	2.2	2.4	1	1
Total change in backfat (mm.)	10.8	8.9	8.8[a]	5.8
Change per yr. (mm.)	1.1	0.7	0.9[a]	1.2
Change per generation (mm.)	2.4	1.8	0.9[a]	1.2
Reference	Present paper	Jonsson (1965)	Hetzer *et al.* (1963)	Gray *et al.* (1965)

[a] Measured as a deviation from a random bred control.

their records and pedigrees can combine to effect a rapid rate of improvement in breed performance not only for one character but for several economic traits concurrently? Determining the real nature of the trends in performance is an important task for animal geneticists and for the swine industry. The most satisfactory method in pigs would probably be to establish random-bred control herds and use these to measure the genetic changes being achieved.

Summary

Data from an experimental herd, maintained by boars purchased from breeders involved in the Iowa swine testing program, were used to assess the importance of genetic herd differences and to estimate genetic trends in the breeds. Genetic herd differences were found to account for a very small portion of the total variance in gain and fatness. Estimates of genetic trends (from regressions of adjusted progeny performance on age of dam within periods) were much smaller than the trends in performance at the testing stations and even different in sign.

A questionnaire was sent to breeders to assess what criteria they used in their choice of breeding stock. There was considerable exchange of stock among herds and also among states. Type and appearance were the most important items in selecting boars, while performance test records had a lower priority. The dilemma, having large phenotypic changes in performance contrasted with low estimates of genetic change and little evidence of selection, needs to be resolved.

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APPENDIX

QUESTIONNAIRE TO BREEDERS

We would like to learn your reasons for the purchase and use of boars in your herd. We are sending this questionnaire to all breeders who are testing boars at the Ames Testing Station. Could you answer the following questions: (1) for the sire of your group on test and (2) for the youngest boar in service in your herd.

	Sire of your group on test	Your youngest boar in service
Name		
Year of birth		
Name and address of breeder		
bought (used) this boar because of:	(Rank your reasons 1, 2, 3)	
his type and appearance		
his own performance record (give his index or record)		
his sire's performance record (give his index or record)		
his brother's performance record (give his index or record)		
his pedigree		
his herd of origin		
his (price, availability, feet and legs, etc.)		

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QUANTITATIVE STUDIES ON BLOOD GROUP AND SERUM PROTEIN SYSTEMS IN PIGS. I. SEGREGATION RATIOS AND GENE FREQUENCIES [1]

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FIFTEEN blood group and seven serum protein systems have been identified in the domestic pig. However, the significance of these polymorphisms in pig populations is still undetermined. The problem was studied using data on 17 blood systems together with pedigree and performance records on the same pigs. The relative viabilities of different genotypes or phenotypic classes were studied using segregation data from known matings. The changes over a period of time in gene frequency at the various loci were examined to study the dynamics of these simple genetic systems. The effects of the systems on production and reproduction are reported in a second paper (Jensen *et al.*, 1968).

Materials

Data used in this study were collected from 1961 to 1966 in an experimental herd used to study the genetic effects of paternal irradiation in pigs. The general design and objectives of the project were given by Willham and Cox (1962). Study of the blood and serum groups was included to measure mutation rates at specific loci in irradiated and control groups. The irradiation treatments are ignored in this study. The pigs were purebred, either Duroc or Hampshire, and were farrowed in two separate 6-wk. periods in each year. A new set of males, 15 pairs of full brothers per breed, was purchased from pedigree pig breeders in Iowa and used to sire the pigs in each period. Replacement females were kept from first and second parity dams in the herd, while older dams were culled at random, irrespective of their reproductive status. Each litter was raised in one pen to 154 days of age, and there was no culling of piglets during the test. Blood samples were taken from the piglets at birth in the first seven periods. No sampling was done in the eighth period. In the last three periods, blood samples were taken for both red cells and serum at 42 days of age (weaning). The red cell typing procedures used were described by Andresen (1963). The starch gel electrophoretic techniques used were given by Baker (1968a).

The systems involved, the number of distinct reagents used for each factor, and the period of study for each system are given in table 1. Three pairs of loci are linked: *C* and *J*, $\hat{\theta}=5.3\%$ (Andresen and Baker, 1964); *I* and *Am*, $\hat{\theta}=0.8\%$ (Andresen, 1966a); and *K* and *Hp*, $\hat{\theta}=3.6\%$ (Andresen, 1966b), where $\hat{\theta}$ is the estimated recombination percentage. Seven of the blood group systems (A, C, F, H, J, K, M) are termed "open" because some pigs did not react to any of the reagents available for these systems. Such individuals are given the symbol –/–. In the open systems, a homozygote a/a cannot be distinguished from a heterozygote a/– except by a progeny test. Five blood group systems (B, E, G, I, L) and all five serum systems are called "closed" because the blood of all pigs reacts with at least one reagent or exhibits at least one band on the starch gel. With the exception of the A system (Rasmusen, 1964), and those with only one reagent, the alleles function as co-dominants. Thus, in the closed systems, the genotypes of all pigs could be determined from the phenotype or laboratory test.

Questionable serological test reactions or starch gel interpretations (less than 1%) were repeated. Errors in classification were detectable only if offspring with unexpected phenotypes were produced. These, and their parents, were then subjected to further testing and the individuals concerned were reclassified if in error. After exhaustive checking, only two anomalous pigs remained (Andresen, 1967; Baker, 1968b).

The total data available was on about 16,000 pigs from over 2,000 litters, the progeny of 429 sires.

Segregation Data. In any system, the pheno-

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TABLE 1. GENE FREQUENCIES IN 17 SYSTEMS IN TWO BREEDS AND THEIR TRENDS OVER TIME

System	Allele	Yr. tested	Reagents used[a]	Duroc			Hampshire		
				No. of animals	Gene frequency	Regression of gene frequency on yr.	No. of animals	Gene frequency	Regression of gene frequency on yr.
A	A^{-}†	5.5	..	948[b]	0.71	—0.016	1003[b]	0.69	—0.01
	A^{A}	...	2	....	0.29	0.016	....	0.31	0.01
B	B^{a}	5	2	7579	0.73	—0.014	7789	0.91	—0.00
	B^{b}	...	2	....	0.27	0.014	....	0.09	0.00
C	C^{-}	4.5	..	6990	0.86	0.025	7048	1.00	.....
	C^{a}	...	2	....	0.14	—0.025	....	....[c]	.....
E	E^{dbg}	5.5	..	7614	0.20	—0.004	8293	0.53	—0.01
	E^{deg}	...	..	....	0.34	—0.015	....	0.07	—0.00
	E^{aeg}	...	14	....	0.09	0.004	....	0.40	0.02
	E^{def}	...	..	....	0.37	0.017	....	0.00[c]	.....
	E^{eg}	...	..	....	....	.....	....	0.00	.....
F	F^{-}	5.5	..	8331	0.90	0.008	8392	0.67	—0.01
	F^{a}	...	3	....	0.10	—0.008	....	0.33	0.01
G	G^{a}	5.5	3	7103	0.52	—0.012	7002	0.72	0.02
	G^{b}	...	3	....	0.48	0.012	....	0.28	—0.02
H	H^{-}	4.5	..	6982	....	.....	6986	0.81	—0.00
	H^{a}	...	2	....	0.52	0.012	....	0.17	0.00
	H^{c}	...	2	....	0.48	—0.012	....	0.02	—0.00
I	I^{a}	4.5	1	7005	0.33	—0.016	7045	0.60	—0.02
	I^{b}	...	2	....	0.67	0.016	....	0.40	0.02
J	J^{-}	3.5[d]	..	2224	0.76	.....	2289	0.68	.....
	J^{a}	...	1	....	0.24	.....	....	0.32	.....
K	K^{-}	5.5	..	8308	0.09	—0.016	8391	....	.....
	K^{a}	...	3	....	0.49	0.014	....	0.19	—0.00
	K^{b}	...	6	....	0.42	0.002	....	0.81	0.00
L	L^{a}	5.5	..	5061	0.79	0.003	4647	0.21	—0.00
	L^{b}	...	..	....	0.02	0.001	....	0.56	0.00
	L^{bce}	...	15	....	0.20	—0.006	....	0.12	—0.00
	L^{ac}	...	..	....	0.00	—0.001	....	0.11	—0.00
M	M^{-}	2.5[d]	..	3489	0.77	.....	3303	0.56	.....
	M^{d}	...	1	....	0.23	.....	....	0.44	.....
Amylase									
	Am^{A}	1.5[d]	..	2877	....	.....	2351	0.09	.....
	Am^{B}	...	..	....	1.00	.....	....	0.90	.....
	Am^{C}	...	..	....	....	.....	....	0.01	.....
Ceruloplasm									
	Cp^{a}	1.5[d]	..	2877	1.00	.....	2351	1.00	.....
	Cp^{b}	...	..	....	....	.....	....	....	.....
Hemopexin									
	Hp^{0}	1.5[d]	..	2877	....	.....	2351	0.21	.....
	Hp^{1}	...	..	....	0.32	.....	....	0.62	.....
	Hp^{2}	...	..	....	0.10	.....	....	0.08	.....
	Hp^{3}	...	..	....	0.58	.....	....	0.09	.....
	Hp^{4}	...	..	....	....	.....	....	0.00	.....
Pre-albumin									
	Pa^{A}	1.5[d]	..	2877	0.51	.....	2351	0.31	.....
	Pa^{B}	...	..	....	0.49	.....	....	0.69	.....
Transferrin									
	Tf^{A}	1.5[d]	..	2877	0.23	.....	2351	0.20	.....
	Tf^{B}	...	..	....	0.77	.....	....	0.80	.....
	Tf^{E}*	...	..	....	....	.....	....	0.00	.....

[a] Sera from different donors.
† Reagent a^{a} was not used.
[b] Dams, all other systems refer to progeny.
[c] (....) allele not present; (0.00) allele found but at low frequency.
[d] Too few years to estimate trends.
* Tf^{E} Ames.

typic distribution of progeny from each parental mating type ought to follow a simple Mendelian ratio. Comparison of observed and expected numbers will provide a check on Mendelian inheritance, or if the theory is assumed, will give a measure of the relative viability of different phenotypes at each system.

The distribution of progeny from each mating type was examined for the progeny available at the time of typing and also for the progeny surviving to 154 days of age, the end of the experimental period. In the open systems, matings were included only if the genotypes of both parents were known or could be inferred from the offspring *in the litter concerned*. For example, at the *C* locus, if an a/? x a/? mating produced one –/– offspring, both parents must be a/–. Selecting only those matings with –/– progeny gives an expected proportion of –/– progeny of $p/(1-(1-p)^n)$, where p is the true frequency of –/– offspring in a/– x a/– matings, and n is the average number of pigs per litter. For example, in detected a/– x a/– matings, the expected proportion of –/– offspring was 0.278 (instead of 0.25), the average litter size being taken as eight. If the genotype of the sire or dam was inferred from other litters, then the amount of bias would be less but it would not be known, so the more precise procedure was adopted. Segregation analysis (Morton, 1959) would make use of all the data, but the method depends on estimates of gene frequency and on the assumption of random mating.

A Chi-square was calculated from the observed and expected numbers of offspring in each mating type for each system and summed to give a total Chi-square as shown in table 2. A summary, from segregating matings, of the total observed and expected numbers at different phenotypes gives an estimate of their relative viability and the pooled Chi-square (table 2) tests the significance of the differences. A Chi-square for heterogeneity among mating types is given by the difference of the total Chi-square and the pooled Chi-square (table 2). The probabilities of obtaining these Chi-squares by chance are given in table 3 along with the number of mating types and number of matings involved.

For most of the systems, deviations from expectation were not significant and the pooled Chi-square probabilities fell throughout the possible range (table 3). For systems not showing significance the following positive conclusions may be drawn: (1) that inheritance was Mendelian, (2) that typing was accurate, and (3) that from conception through birth to 154 days of age, there were no large differences in viability among phenotypes. An alternative, that inheritance was non-Mendelian but appeared so only because of compensating differences in viability, might be tenable for one system but not for 17 systems in two breeds. As a guide to the size of effects detectible, an empirical estimate showed that differences in viability among phenotypes of 5 to 10% could be detected ($P \leq 0.05$) in these analyses, depending on the number of offspring tested and the number of phenotypes in the system. Thus, despite the large numbers

TABLE 2. A SUMMARY OF MATING TYPES AND CHI-SQUARE TESTS FOR THE B SYSTEM IN DUROCS

Mating type		No. of litters	No. of progeny	Offspring phenotypes			Chi-square	d.f.
Sire	Dam			a/a	a/b	b/b		
a/a†	a/a	212	1548	1548	...	...	....	..
a/a	a/b	168	1160	579	581	...	0.00	1
a/a	b/b	30	202	...	202	...	....	..
a/b	a/a	189	1279	629	650	...	0.35	1
a/b	a/b	149	1036	261	540	235	3.17	2
a/b	b/b	24	151	...	79	72	0.33	1
b/b	a/a	26	196	...	196	...	....	..
b/b	a/b	26	187	...	95	92	0.05	1
b/b	b/b	2	17	...	...	17	....	..
					Total Chi-square		3.90	6
Observed totals in segregating matings				1469	1945	399		
Expected totals in segregating matings				1479	1907	428		
					Pooled Chi-square		2.79	2
					Heterogeneity Chi-square		1.11	4

† a/a is B^a/B^a, etc.

TABLE 3. CHI-SQUARE PROBABILITIES FOR DEVIATIONS FROM EXPECTED SEGREGATI NUMBERS AT 154 DAYS OF AGE: (1) POOLED OVER MATING TYPES (2) FOR HETEROGENEITY BETWEEN MATING TYPES AND THE RATIO OF VIABILITY OF HETEROZYGOTES AND HOMOZYGOTES FOR EACH SYSTEM

System	Duroc					Hampshire				
	No. of segregating matings	No. of mating types	Pooled chi-square probability (1)	Heterogeneity chi-square probability (2)	Ratio of viability [a]	No. of segregating mating	No. of mating types	Pooled chi-square probability (1)	Heterogeneity chi-square probability (2)	Ratio viabil
A	224	3	0.85	0.80	1.00	197	3	0.95	0.45	1.0
B	556	5	0.25	0.90	1.04	242	4	0.25	0.45	0.9
C	275	3	0.15	0.45	1.08	....	..	....	....	....
E	722	59	0.20	<0.05*	1.03	759	25	0.40	0.70	1.0
F	285	3	0.15	0.55	0.94	526	3	0.75	0.60	0.9
G	584	5	0.25	0.75	1.05	454	5	<0.05*	0.20	1.0
H	546	5	0.65	0.65	0.98	443	10	0.75	>0.95*	0.9
I	59	3	0.40	0.30	1.03	189	3	0.40	0.80	1.0
J	138	3	0.60	0.40	1.00	148	3	0.10	0.55	0.9
K	248	8	<0.01**	0.40	0.82**	543	5	0.40	0.15	1.0
L	437	15	0.35	0.10	0.97	721	33	0.80	0.50	1.0
M	271	3	<0.01**	<0.01**	0.58**	231	4	<0.05*	<0.01**	0.9
Am	....	..	....	....	....	110	5	0.85	0.75	1.0
Hp	287	19	0.50	0.35	1.07	247	24	0.90	0.06	1.0
Pa	284	5	0.45	0.80	0.95	198	5	0.90	0.40	1.0
Tf	188	5	0.50	<0.01**	0.96	165	6	>0.95*	0.35	1.0

[a] Ratio of viabilities of heterozygotes to homozygotes.
* $P<0.05$.
** $P<0.01$.

of animals available, the tests used were not very sensitive to small differences in viability.

The M system showed significant deviations from expectation at several mating types in both breeds. This was attributed to poor typing reagents for this system, and typing in the M system was discontinued in 1966, before this analysis began. For the other systems, only in two out of 28 tests were there significant pooled Chi-squares ($P\leq0.05$), but the deviations were not consistent between breeds. Of 275 Chi-squares on individual mating types, omitting the M system, 141 tests in Durocs and 134 tests in Hampshires, 14 were significant ($P\leq0.05$). This is the number expected by chance alone at the 5% significance level. Moreover, the deviations from expectation were usually not consistent among mating types nor between breeds.

The viability of heterozygotes and homozygotes was compared for each system in matings with a 1:1 expectation of these classes. The ratios of the numbers in the two classes are given in table 3. In three cases the viability of the classes differed significantly ($P\leq0.05$), differences of 5 to 10% again being required for significance. In general, taking the systems collectively, the evidence does not suggest that heterozygotes of the blood and serum group systems have a superior viability.

There was significant heterogeneity ($P\leq0.05$) among mating types in only two of 28 tests (omitting the M system). For one system (Tf) the heterogeneity could be ascri to differences between reciprocal matin However, of 94 tests among reciprocal matin only two systems, Tf and M, showed signi cant ($P\leq0.05$) divergence. Incompatibility maternal and progeny blood types has b shown in special circumstances in the (Andresen *et al.*, 1965), but the present d indicate it is not a common phenomenon.

Although the segregation ratio tests w used in preference to tests of Hardy-Weinb equilibrium, the latter were also made for closed systems. The Chi-squares, added o periods, were significant ($P\leq0.05$) in 1 14 tests made. Several effects may account the lack of agreement between the two set tests. Robertson (1965) has shown how dif ences in gene frequency between the m (p_m) and female (p_f) parents will always to a surplus of heterozygotes in Hardy-W berg tests, the excess being $(p_m-p_f)^2/2$. T effect may account for some of the disc ancy, for in two-thirds of the cases exam there was an excess of heterozygotes. Ran mating is another condition necessary Hardy-Weinberg equilibrium. However, design of the experiment was to mate set full brothers to several pairs of full siste non-random pattern. Also, each mating duces a litter averaging eight pigs rather a single offspring and this introduces an non-random element. Deviations from Ha Weinberg equilibrium can also be caused differences in fertility among the parents

by parity effects on litter size, associated with the phenotype of the dam. Thus, compared with the segregation ratio tests, the tests of Hardy-Weinberg equilibrium are subject to several biases and are difficult to interpret.

Gene Frequency. The gene frequencies were estimated from all offspring tested over the 5½-yr. period. In the closed systems this was done by counting the alleles and in the open systems the estimate $\sqrt{(1-q)}$ was used, where q was the proportion of phenotypes lacking the allele. The gene frequencies (table 1) in the various systems lie throughout the possible range. Most of the systems satisfy the classical definition of a polymorphism, by their allelic frequencies being at non-trivial levels (>0.01) and by their occurrence in different breeds. The gene frequencies in the two breeds were not similar; four alleles at intermediate frequency in one breed were absent in the other breed. Several of the alleles in the multiple allelic systems were at low frequency, but none were lost from the breeds during the period of study.

To study the dynamics of these simple Mendelian systems over time, separate estimates of gene frequency were made for sires, dams and progeny in each 6-mo. period. In figure 1 the plot of the frequency over time for two of the systems illustrates some of the features of the results. The gene frequencies in the progeny were, as expected, usually intermediate to those of their parents. Small discrepancies may be due to differences in the number of progeny per sire and to poor estimates of gene frequency from sires for the open systems. The plots of the frequencies for sows were fairly stable, since over 100 sows were available in each period and some sows were retained for several parities. By contrast, the frequencies for sires and for progeny fluctuated widely, due to the sampling of sires (15 pairs) from each breed in each period.

Time trends in gene frequency were studied by regressing the gene frequency of progeny on years and the regressions are also given in table 1. Little relation between the trends in gene frequency in the two breeds was noted and the trends were independent of initial gene frequency. In half of the systems the gene frequencies converged, while in the other half they diverged. Several of the regression coefficients indicate important trends in gene frequency. However, these may be due to the effects of sampling of sires and to the initial sampling of the sows in the herd rather than to changes in the gene frequency in the breeds. For example, the trend in the E^{arg} allele in Hampshires (figure 1) is as likely to be due to an atypical initial sample of sows as to a change in the breed. Over a longer period of time, any trend in the breed will be more apparent and sampling effects will be less important.

Discussion

Many authors (e.g., Andresen, 1963) have used small sets of segregation data to confirm the mode of inheritance of new factors or of new genetic systems. The present results represent perhaps a larger set of segregation data than has been available hitherto in pigs and allows unbiassed tests of differential viability. In general, the observed data agree well with Mendelian expectation, indicating that any differences in viability among phenotypes in these systems are less than 5 to 10% and could be zero. Effects smaller than 5 to 10% are perhaps beyond the limits of experimental analysis, because of the insensitivity of tests for binomial data. In studying small differences in viability, the control of any environmental and extraneous factors that may be involved is important. This was conveniently achieved here by doing the analyses within litters, which removed effects due to sire, dam, parity, period, etc. By contrast, the lack of agreement found between Hardy-Weinberg expectations and observed values shows how any unfulfilled assumptions or environmental effects may lead to false conclusions about the relative viabilities of different phenotypes.

These results in pigs contrast with the results of Briles and Allen (1961) and Morton *et al.* (1965) in chickens. The former, in studies of the B system in seven inbred lines, found that heterozygotes were superior to homozygotes by 6% in liveability and 4% in egg production. Morton *et al.* (1965) reported a superiority of 25% in hatchability of heterozygotes over homozygotes at the B locus in a commercial strain of chickens. Kristjansson (1964) found differences in the rate of conception among nine mating types at the transferrin locus in pigs, but this aspect was not tested in the present data.

Sampling variation in the purchase of stock made it difficult to relate the trends in gene frequency in the experimental herd to those in the breeds of origin. However, it would seem worthwhile to continue sampling these

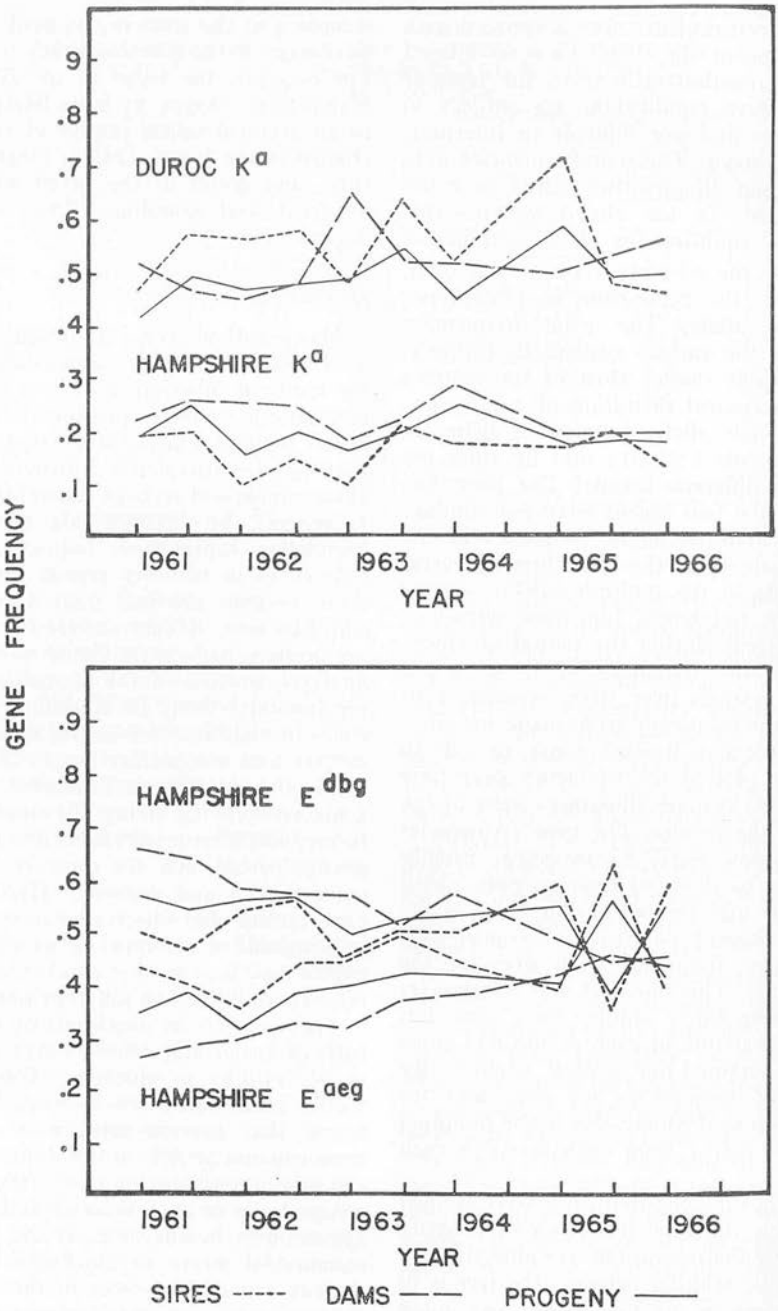

Figure 1. Trends of gene frequency in sires, dams and progeny for two systems.

breeds over a longer period of time to monitor further changes in frequency and to determine if these polymorphisms are of a neutral, balanced or transient form.

A comparison of their gene frequencies provide a guide to the relationships a breeds. Matoušek (1966) reported estim of gene frequency in many of the sy

TABLE 4. CORRELATIONS OF GENE FREQUENCIES OF 18 ALLELES FOR 15 SYSTEMS IN SIX PIG BREEDS[a]

	Large White	Black & White-Prestice	Cornwall	Hampshire	Duroc
Black & White-Prestice	0.89	....	....	....	....
Cornwall	0.71	0.90	....	....	....
Hampshire	0.64	0.75	0.79	....	....
Duroc	0.49	0.66	0.56	0.41	....
Landrace	0.59	0.62	0.62	0.57	0.45

[a] From Matoušek (1966) and present paper.

studied here for four pig breeds in Czechoslovakia. Simple correlations among the gene frequencies in 15 systems in these breeds and in the Duroc and Hampshire are given in table 4. Of all combinations the Duroc and Hampshire had the lowest correlation between their gene frequencies. The Duroc and Landrace both had a rather distinct set of frequencies, while there was more resemblance among the frequencies, perhaps indicating similar ancestry, of the other four breeds.

The presence of these polymorphic systems in several breeds of pigs is not unexpected. The systems studied here are not a random sample, since to be discovered they had to be segregating in some pig population. The Duroc and Hampshire breeds were formed some 70 to 80 yr. ago in the USA (Briggs, 1958). The foundation material and early history of the breeds are not well documented, but the origins seem to have been quite heterogenous. The accumulated inbreeding in both breeds is estimated at about 15%, assuming ½% inbreeding per generation of 2½ yr. This is also the percentage of the original segregating loci, with neutral effects, that would be expected to be fixed by now in these breeds. So segregation in many systems would be expected if the original foundation stocks were heterogenous. By contrast a line of Poland China, presently maintained at Iowa State University and inbred 80 to 90%, was found to be segregating in only two of the systems studied here, the F system and the Pa system, neither of which had significant effects on viability in this study. Thus, although many other causes are possible, the existence of the blood and serum group polymorphisms in these breeds today may be simply accounted for by the heterogenous origin of the breeds.

Summary

Segregation data of progeny from known matings were studied for 12 blood group systems and five serum polymorphisms in two breeds of pigs. A total of some 16,000 pigs from 429 sires was available. The viability of different phenotypes in each system was compared for all pigs alive at 154 days of age. Most of the segregation numbers did not differ significantly from expectation showing that: (1) inheritance was Mendelian, (2) typing was accurate, and (3) any differences in viability from conception through birth to 154 days, are less than the 5 to 10% level detectable ($P \leq 0.05$) by these experimental data. In cases showing significant deviations (14 out of 275 mating types), the results were inconsistent among mating types and between breeds. Homozygotes and heterozygotes had similar viabilities.

Most of the systems are truly polymorphic in that the alleles have non-trivial frequencies and occur in several breeds. Trends in gene frequency which could reflect changes in the breeds were studied. The frequencies fluctuated over the 5½ yr. involved, but due to sampling effect in purchase of breeding stock it was not possible to establish if any real trends had occurred.

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QUANTITATIVE STUDIES ON BLOOD GROUP AND SERUM PROTEIN SYSTEMS IN PIGS. II. EFFECTS ON PRODUCTION AND REPRODUCTION [1, 2]

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TWELVE blood group and four serum protein systems were studied to determine relationships with 10 performance traits in pigs. The two basic questions posed in this analysis were: what effects do these systems have on performance traits, and what is their usefulness in selection and pig improvement?

Materials

The data were described by Smith *et al.* (1968) and only special features, relevant to this study, will be repeated.

Data were available on some 16,000 Duroc and Hampshire pigs, from over 2,000 litters sired by 429 males. Each litter was kept in the same pen from birth to 154 days of age, when the test ended. Male pigs were castrated at 1 to 2 wk. of age. Litters were weaned at 42 days of age and were self-fed during finishing. No fostering or culling of piglets was allowed, and any culling among females, to maintain herd size, was at random.

For the serum protein systems and five of the blood group systems, the genotypes of all individuals could be determined by the laboratory tests. However, for the seven "open" blood group systems, the homozygote (a/a) could be distinguished from the heterozygote (a/–) only by a progeny test. Individuals were coded a/? where the zygosity was not known. If the genotype of an individual could be inferred from the genotypes of its relatives, then the inferred genotype was used. By using inferred genotypes, bias could be introduced. However, since the probability of making errors was very low, the possible bias was considered to be negligible.

Ten traits were studied, five representing aspects of growth and fatness (production traits) and five being measures of reproductive performance. The traits, along with means and standard deviations, are listed in table 1. Correlations among traits within the productive and reproductive groups are also included. These correlations indicated dependencies among measures of pig weight and among measures of litter size. Birth weight was measured on all pigs born alive (as judged by lung dilation); length of life ranged from zero to 154 days. Average backfat probe at the shoulder, back, and loin was adjusted for 154 day weight; the regression coefficients were 0.39 mm./kg. for Durocs and 0.32 mm./kg. for Hampshires. The reproductive traits were measured on all litters in which any pigs, dead or alive, were farrowed. The correlations among the traits within each group are also given in table 1 showing that there are dependencies among the measures of pig weight and among the measures of litter size.

It was important to eliminate environmental and other sources of variation in estimating the effects of these systems on performance traits. This was conveniently done for the productive traits by performing least squares analyses within litters. The five productive traits were observations on individual pigs. The model for the least squares analysis was then:

$$y_{ijkl}=\mu+l_i+s_j+b_k+e_{ijkl} \qquad (1)$$

where μ is the population mean, l_i is the effect of the i^{th} litter, s_j is the effect of the j^{th} sex, b_k is the effect of the k^{th} blood or serum group phenotype and e_{ijkl} is a random effect of the l^{th} individual. Least squares equations for the mean (μ) and for litters (l_i) were absorbed into the equations for sex and phenotype. This is equivalent to comparing pigs within litters and thus eliminates the effects of parents, pens, seasons, and other environmental effects common to a litter. All tested pigs were used for traits 1 and 2, but only those which lived to 154 days of age were used for traits 3 to 5.

The classification models used for the reproductive traits also attempt to exclude extraneous source of variation but do so less satisfactorily than does model (1). The main model was

[1] Journal Paper No. J-5778 of the Iowa Agricultural and Home Economics Experiment Station, Ames. Project No. 1424. This work has received assistance from Contract AT(11-1)-707 with the U. S. Atomic Energy Commission.
[2] We are grateful to Dr. Erik Andresen and Derald Kimm for their extensive and accurate blood typing work.

TABLE 1. MEANS, STANDARD DEVIATIONS AND CORRELATIONS AMONG TRAITS AVERAGED OVER BREEDS

Item	Mean	Standard deviation	Correlations: Trait 2	Trait 3	Trait 4
Productive traits					
1. Length of life (days) [a]	128.9	53.5	0.29	....	....
2. Birth wt. (kg.)	1.28	0.29	....	0.49	0.35
3. Wt. at 42 days of age (kg.)	11.03	2.70	....	....	0.60
4. Wt. at 154 days of age (kg.)	79.5	15.5	....	....	....
5. Av. backfat probe (mm.)	28.9	4.7	....	....	....

Item	Mean	Standard deviation	Correlations: Trait 7	Trait 8	Trait 9
Reproductive traits					
6. No. of regressing fetuses	0.39	0.77	0.77	—.04	—.07
7. No. born dead	0.74	1.25	....	—.17	—.24
8. No. born alive	9.55	2.72	....	....	0.75
9. No. alive at 6 days	7.98	2.62	....	....	....
10. No. alive at 42 days	7.08	2.75	....	....	....

[a] ≤154 days.

$$y_{ijkl}=\mu+t_i+p_j+b_k+e_{ijkl} \qquad (2)$$

where t_i is the effect of the i^{th} consecutive 6-mo. period, p_j is the effect of the j^{th} parity group, and the other symbols are the same as in model (1). Equations for the mean (μ) and periods (t_i) were absorbed into the remaining equations. Several sources of variation, such as sires, mates and interactions of period and parity, were not eliminated by this model. A further model was used comparing performance of females within sires. Since sires were used for only one period, their daughters in any one period were of the same parity. The model then was

$$y_{ijkl}=\mu+t_i+sr_{ij}+b_k+e_{ijkl} \qquad (3)$$

where t_i is the effect of the i^{th} period and sr_{ij} is the effect of the j^{th} sire on his daughters farrowing in the i^{th} period. The $(\mu+t_i+sr_{ij})$ equations were absorbed into the remaining equations. Unfortunately, this partition of the data greatly reduced the number of comparisons available.

The effect of service sire (mate) was not included in Models (2) and (3). Smith *et al.* (1968) concluded that there was no evidence for incompatibility of maternal and progeny blood types in these data. Because of complexity and computing costs, interactions among loci were ignored. Several systems were analyzed simultaneously and results were compared with those from analyzing each system alone. There were only small differences, which lended support to the assumption that systems are independent.

The portion of the total variance in a tr that can be attributed to the blood and ser systems individually and collectively was e mated approximately by the following meth The total variance was defined as the varia remaining after absorption of the litter eq tions for the productive traits and of t period equations for the reproductive tra The analysis of variance was of the fo shown in table 2. The portion of the to variance (P_i) due to the blood or serum s tem (i) can be estimated approximately

$$\hat{P}_i \simeq \frac{(MS_b - MS_e)}{k_i MS_t} \simeq \frac{F_i - 1}{k_i}$$

assuming $MS_e \simeq MS_t$, as is the case when t component σ^2_b is small. The portion of t total variance (P) in a trait attributed t independent blood and serum systems is t approximately $\hat{P} \simeq \sum_{i=1}^{n} \frac{F_i - 1}{k_i}$, with varia

$V(\hat{P}) \cong 2\sum_{i=1}^{n} \frac{1}{k_i 2b_i}$, since the variance ra (F_i), with a large number of degrees of f

TABLE 2. BASIC ANALYSIS OF VARIANCE F EACH SYSTEM WITHIN BREEDS

Source	d.f.	Mean square	Expectation	Vari
System	b	MS_b	$\sigma^2_e + k\sigma^2_b$	
Residual	e	MS_e	σ^2_e	
Total	t	MS_t		

dom for the denominator mean square, are distributed as χ^2_i/b_i and the variance of χ^2_i is $2b_i$.

Discussion

The problem of summarizing the large number of results from the least squares analyses was approached as follows. First, the F-tests for each system-trait combination were examined and summarized. Then the effects for systems with significant F's were studied and compared in the two breeds. Finally the variation due to the systems, individually and collectively, was estimated for each trait.

Table 3 shows the probability level of obtaining the observed F-test value by chance alone for each system-trait combination. For example, for the A system in Durocs, with two phenotypes, the F value with one degree of freedom for length of life (trait 1) was 0.62. The probability of getting an F value as large or larger than this by chance is 0.54, the value in table 3. In general, the F values fell throughout the whole probability range, showing that most of the systems were not influencing the traits being studied. However, there was an excess of tests at the low probability end of the distribution (figure 1). Of 150 F-tests made in each breed, 21 were significant ($P \leq 0.05$) in Durocs and 17 in Hampshires. This is twice the number that would be expected if there were no influence of blood and serum systems on the traits being studied. Similarly at the 0.01 probability level, some 13 F-tests were significant while only three would be expected. The excess of significant F-tests was similar for the two sets of traits. If the blood and serum systems had no effect on these traits, the F values should have a uniform distribution with mean 0.50 and variance 0.0833. The over-all average in table 3 was 0.40 ($P < 0.01$) for Durocs and 0.46 ($P = 0.05$) for Hampshires and the variances were 0.0861 and 0.0935, respectively. These deviations, together with the excess of significant F-tests, indicate that the blood and serum system classifications were in some way associated with the traits being studied.

A useful summarization of the F-test results is given by the row and column averages of table 3. A row average reflects an average influence of a system on the array of traits being studied, while a column average reflects an average influence of the array of systems on a particular trait. When averaged over all traits, the C, H and J Systems in Durocs, and the E and H systems in Hampshires showed significant ($P \leq 0.05$) deviations. Two systems showed significance for productive traits and five showed significance for reproductive traits for Durocs. Corresponding figures for Hampshires were one and four. Four traits showed significant deviations across systems (columns) for Durocs, but there were none for Hampshires. The grand average was highly significant ($P < 0.01$) for Durocs and was significant ($P = 0.05$) for Hampshires.

How reliable is the F-test in one breed as a guide to the outcome in the other breed? The simple correlation of the F-test probabilities in the two breeds was 0.08 ± 0.08, indicating a lack of consistency between breeds. In only five cases was there significance ($P \leq 0.05$) at the same system-trait combination in both breeds. It appeared that differences in gene frequency in the two breeds had little effect on the consistency of F-test values across breeds.

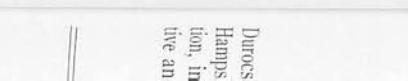
The least squares constants of the effects of different phenotypes were also obtained in the analyses. These will not be reported in detail but are available on request from the authors. The size of the effects at the various systems can, however, be gauged from the F-test probabilities in table 3; the lower the probability level the greater the differences among phenotypes. As a guide to the size of the effects, the average range between the best and worst phenotypes in systems with significant F-tests was about 0.21 standard deviations for the productive traits and 0.35 standard deviations for the reproductive traits. Thus, there were substantial differences between phenotypes in some systems. However, where direct comparisons were possible between breeds, the effects of the phenotypes were consistent in sign in only about half of the cases. Because of this, less confidence was placed on the estimates than their sampling variances indicated.

The effects of two systems are shown in table 4, one showing consistent effects, the other inconsistent effects in the two breeds. At the H system the H^a allele was superior to the H^c allele for weight in both breeds while the reverse was true for the reproductive traits. The H^- allele (in Hampshires only) was intermediate for both sets of traits. There were also large effects on reproductive traits at the E system in both breeds, but the array of phenotypes was different in the two breeds. At the Tf system the Tf^B allele was superior to the Tf^A allele for 42- and 154-day weight in

TABLE 3. PROBABILITY LEVEL OF OBTAINING THE OBSEVED F-TEST VALUE BY CHANGE ALONE FOR 16 BLOOD AND SERUM SYSTEMS ANALYZED ON 10 TRAITS IN TWO BREEDS. INCLUDED ARE THE NUMBER OF PHENOTYPES AND NUMBER OF PIGS TYPED FOR EACH SYSTEM

	Productive traits[a]								Reproductive traits[a]								
System	No. of phenotypes	No. of pigs	1	2	3	4	5	Av. of traits 1–5	No. of phenotypes	No. of pigs	6	7	8	9	10	Av. of traits 6–10	Av. of 10 traits
A	3[b, d]	2523	0.54	0.23	0.03	0.60	0.77	0.43	2	747	0.74	0.58	0.005	0.05	0.27	0.33	0.38
	3[c]	1965	0.93	0.22	0.16	0.06	0.01	0.28*	2	930	0.82	0.48	0.43	0.53	0.84	0.62	0.45
B	3	5261	0.92	0.73	0.08	0.11	0.87	0.54	3	729	0.33	0.30	0.33	0.40	0.64	0.40	0.47
	3	5068	0.96	0.66	0.24	0.29	0.50	0.53	2	711	0.61	0.005	0.9999	0.45	0.16	0.44	0.49
C	3	5261	0.26	0.97	0.06	0.05	0.005	0.27*	2	729	0.35	0.04	0.10	0.22	0.35	0.21**	0.24**
..	..	....	....	....	....	....	....	....	..	...	....	....	....	....	...	....	....
E	9	6042	0.77	0.64	0.32	0.67	0.55	0.59	6	747	0.15	0.48	0.05	0.08	0.15	0.18**	0.39
	5	6171	0.01	0.65	0.05	0.22	0.72	0.33	5	930	0.83	0.72	0.04	0.02	0.04	0.33	0.33**
F	3	6042	0.58	0.44	0.63	0.90	0.49	0.61	2	747	0.04	0.73	0.83	0.68	0.68	0.59	0.60
	3	6171	0.76	0.48	0.38	0.55	0.45	0.52	2	930	0.9999	0.18	0.43	0.12	0.06	0.36	0.44
G	3	2644	0.04	0.46	0.18	0.09	0.77	0.31	3	747	0.72	0.68	0.35	0.04	0.14	0.39	0.35
	3	2616	0.12	0.42	0.85	0.97	0.06	0.48	3	930	0.70	0.13	0.36	0.03	0.06	0.25**	0.37
H	3	5261	0.58	0.47	0.005	0.0005	0.72	0.36	3	729	0.69	0.44	0.0005	0.0005	0.0005	0.23**	0.29**
	4	5068	0.55	0.12	0.56	0.60	0.94	0.55	3	711	0.34	0.11	0.04	0.08	0.03	0.12**	0.34*
I	3	5261	0.31	0.01	0.54	0.78	0.15	0.36	3	729	0.62	0.52	0.25	0.54	0.54	0.49	0.43
	3	5068	0.31	0.13	0.64	0.66	0.64	0.48	3	711	0.51	0.84	0.33	0.85	0.62	0.63	0.55
J	3	2211	0.15	0.15	0.12	0.26	0.13	0.16**	2	490	0.47	0.32	0.11	0.02	0.19	0.22**	0.19**
	3	2248	0.32	0.68	0.43	0.51	0.61	0.51	2	560	0.05	0.61	0.67	0.60	0.88	0.56	0.54
K	7	6042	0.16	0.04	0.19	0.99	0.09	0.29	3	747	0.96	0.26	0.66	0.23	0.78	0.58	0.44
	3	6171	0.27	0.72	0.43	0.10	0.14	0.33	3	930	0.34	0.99	0.77	0.65	0.69	0.69	0.51
L	3	5261	0.41	0.34	0.22	0.01	0.73	0.34	2	729	0.9999	0.95	0.11	0.9999	0.86	0.78	0.56
	9	5068	0.86	0.84	0.75	0.42	0.37	0.65	4	711	0.25	0.91	0.35	0.04	0.005	0.31	0.48
M	3	2644	0.23	0.21	0.70	0.87	0.59	0.52	2	381	0.66	0.46	0.56	0.09	0.17	0.39	0.45
	3	2616	0.41	0.31	0.96	0.39	0.53	0.52	2	382	0.24	0.95	0.33	0.9999	0.90	0.68	0.60
Am	..	....	....	....	....	....	....	....	..	...	....	....	....	....	....	....	....
	3	1965	0.62	0.69	0.81	0.46	0.05	0.53	2	252	0.74	0.21	0.04	0.13	0.20	0.26**	0.40
Hp	5	2523	0.46	0.89	0.59	0.40	0.05	0.48	5	359	0.88	0.09	0.63	0.26	0.41	0.45	0.47
	8	1965	0.91	0.60	0.03	0.11	0.61	0.45	3	252	0.15	0.42	0.85	0.86	0.55	0.57	0.51
Pa	3	2523	0.49	0.84	0.67	0.46	0.09	0.51	3	359	0.32	0.24	0.30	0.17	0.26	0.26**	0.38
	3	1965	0.35	0.74	0.50	0.94	0.30	0.57	2	252	0.43	0.15	0.06	0.09	0.14	0.17**	0.37
Tf	3	2523	0.69	0.44	0.14	0.03	0.63	0.39	3	359	0.94	0.06	0.23	0.36	0.68	0.45	0.42
	3	1965	0.63	0.77	0.07	0.05	0.98	0.50	3	252	0.51	0.20	0.24	0.72	0.68	0.47	0.49
Column means			0.44	0.46	0.30**	0.42	0.44	0.41**			0.59	0.41	0.30**	0.28**	0.41	0.40**	0.40**
			0.53	0.54	0.46	0.42	0.46	0.48			0.50	0.46	0.40	0.41	0.39	0.43**	0.46*

[a] See Table 1 for identification of traits.
[b] Duroc.
[c] Hampshire.
For row and column means, *P≤0.05, **P≤0.01 that true means do not differ from 0.50.
[d] The identity and frequency of the phenotypes can be obtained from Table 1 in the first paper in this series (Smith *et al.*, 1968).



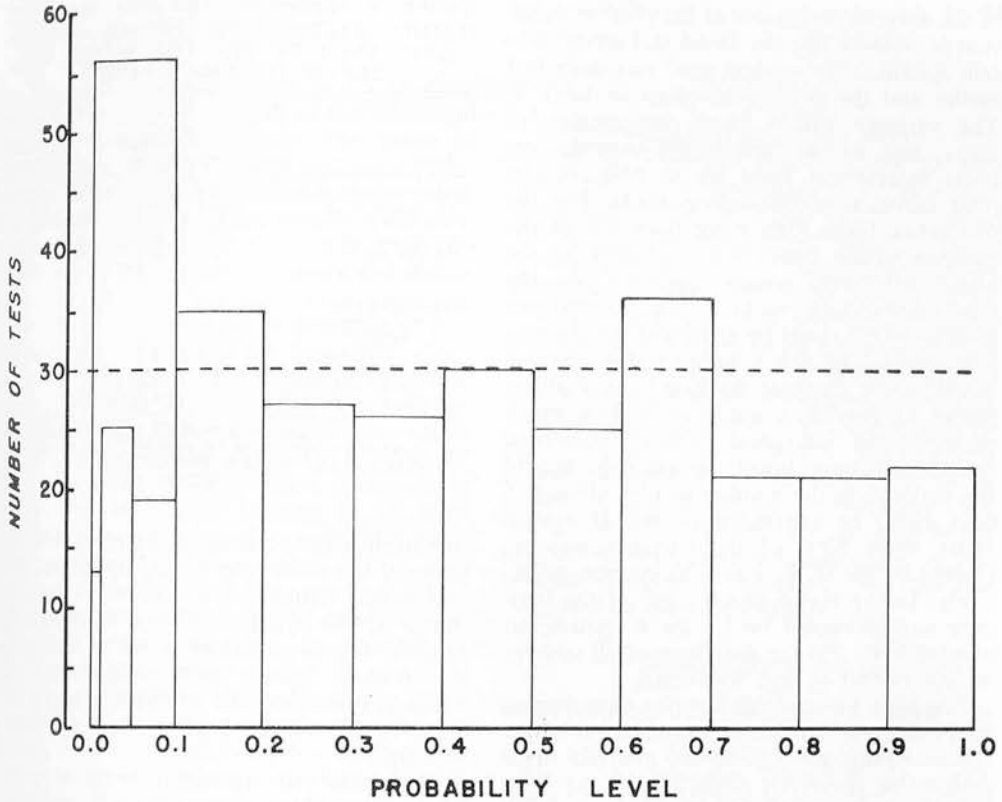


Figure 1. Distribution of the probabilities for 300 F-tests. Expected number in each class (dotted line) was 30.

Durocs, but the reverse was found in the Hampshire breed. Several types of gene action, including all levels of dominance (positive and negative) were found but none predominated. Hence, no generalization can be drawn about the distribution of gene effects for these blood and serum systems.

A third, and perhaps more general summary

TABLE 4. LEAST SQUARES ESTIMATES FOR PHENOTYPES AT THE H BLOOD GROUP AND TF SERUM PROTEIN SYSTEMS[d]

		Trait									
		42-day wt. (kg.)		154-day wt. (kg.)		No. born alive		No. alive at 6 days		No. alive at 42 days	
System	Phenotypes	D[a]	H[b]	D	H	D	H	D	H	D	H
H	a/a	0.14**	....	0.75**	....	−.83**	....	−.77**	....	−.57**	....
..	a/c	0.09	....	0.77	....	0.17	....	0.15	....	0.04	....
..	c/c	−.23	....	−1.52	....	0.66	....	0.62	....	0.53	....
..	−/−	....	−.03	....	0.08	....	−.20*	....	−.33†	....	−.42*
..	a/−	....	0.10	....	0.73	....	....	....	....	....	....
..	a/?	....	0.06	....	0.04	....	−.56	....	−.43	....	−.54
..	c/−, c/?	....	−.13	....	−.85	....	0.76	....	0.76	....	0.96
Tf	A/A	−.15	0.31†	−2.51*	0.81*	No significant * effects					
..	A/B	−.04	0.01	0.58	0.86						
..	A/B	−.04	−.01	0.58	0.86						
..	B/B	0.19	−.30	1.93	−1.67						

† P≤0.10.
* P≤0.05.
** P≤0.01 by F-test.
[a] Duroc.
[b] Hampshire.
[d] Least squares estimates for other systems are available on request from the authors.

For row and column means, * P≤0.05, ** P≤0.01 that true means do not differ from 0.50.
d The identity and frequency of the phenotypes can be obtained from Table 1 in the first paper in this series (Smith *et al.*, 1968).

of the data, is the percent of the total variance that is explained by the blood and serum protein systems. The method used was described earlier and the results are given in table 5. The variance within litters for productive traits, and within periods for reproductive traits represented from 85 to 95% of the total variance in the various traits. For the productive traits little more than 1% of the variance within litters was explained by the blood and serum groups. However, for the reproductive traits, up to 12% of the variance within periods could be attributed to the systems studied. Of this a large portion was due to only a few systems; the F-test probabilities (table 3) provide a guide as to how much variation the individual systems accounted for. In the Duroc breed, for example, 6% of the variance in the number of pigs alive at 6 days could be attributed to the H system alone, while 10% of the variance was explained by the G, H, J and M systems collectively. In the Hampshires, 6.8% of the variance was accounted for by the B system out of a total of 8.2% for the effects of all systems on the number of pigs born dead.

The least squares analyses for reproductive traits discussed so far used model (2). Model (3) was more restrictive, the analysis being within sire groups of dams having the same parity. However, this restriction more than halved the degrees of freedom available so that the least squares constants were measured with much less precision. With model (3), the systems explained a much smaller percent of the total variance than before, and the least squares effects were also smaller. However, the ranking of the phenotypes was similar with the two models. These results raise the question as to the appropriateness of either analysis, one having possible biases and the other lacking in precision.

Only a few studies are available on the association of blood and serum groups with economic traits in pigs. Baltzer (1964) analyzed relationships of 17 red blood cell factors with growth and carcass traits in progeny testing data in Germany. Of 1,122 t-tests, 9.3% were significant ($P \leq 0.05$). Schrape (1966) worked with additional data from the same source and found, using a within sire analysis, that 7.8% of some 2,654 t-tests were significant ($P \leq 0.05$). If the level of significance is adjusted (e.g., Niemann-Sørensen and Robertson, 1961) to account for the large number of tests (since by chance, one in 20 might be expected to be significant at $P \leq 0.05$), very few

TABLE 5. PERCENT OF THE VARIANCE WITHIN LITTERS, OR WITHIN PERIODS, EXPLAINED BY ALL THE BLOOD AND SERUM SYSTEMS STUDIED[a]

Items	Duroc		Hampshire	
	%	Standard error	%	Standard error
Productive traits				
1. Length of life	0.2	0.4	−.5	0.6
2. Birth wt.	0.2	0.4	−.6	0.6
3. 42-day wt.	1.3	0.5	0.6	0.6
4. 154-day wt.	1.2	0.5	0.7	0.6
5. Av. backfat probe	1.0	0.5	1.3	0.6
Reproductive traits				
6. No. of regressing fetuses	−2.6	2.5	−1.0	3.6
7. No. born dead	3.7	2.5	8.2	3.6
8. No. born alive	10.8	2.5	7.4	3.6
9. No. alive at 6 days	12.4	2.5	3.8	3.6
10. No. alive at 42 days	3.2	2.5	5.3	3.6

[a] Percent of variance within litter for productive traits, percent of variance within period for reproductive traits. Variance within classifications was 85 to 95% of the total variation in traits.

significant effects remained. However, because many of the traits were highly correlated, this adjustment probably is too restrictive (as shown by the hypothetical case of repeatedly running the same test on a set of data). In the present study, using within-litter or within-period analyses of larger groups of data, 12.6% of the F-tests were significant ($P \leq 0.05$).

There was little agreement between the effects of the blood group factors reported by Baltzer (1964) and Schrape (1966). For example, Baltzer found effects of the M_a factor on gain and efficiency in several sub-groups while Schrape did not. In the work reported here, the effects of phenotypes rather than blood group factors were studied, but where some comparison was possible (154-day weight and backfat probe), little agreement with either previous report was found.

The percent of the variance in traits explained by the blood and serum group systems provides a guide to their usefulness in selection (e.g., Smith, 1967). This percent was quite small (less than 2%) for the production traits indicating that these systems would be of little value in the improvement of these traits. However, for the reproductive traits from 0 to 12% of the within period variance was explained using Model (2). Since the heritabilities of reproductive traits are low (5 to 15%), these systems may provide an alternate means of improving reproductive performance. However, it is unexpected and unlikely that the genetic variance due to these systems could be as large as the heritability (the total additive genetic variance

unless much of the former was dominance variance which is not included in the heritability estimates.

The most consistent effect found in these analyses was the large effect of the H system on reproductive performance, the range in performance between the best and worst phenotypes being about half a standard deviation. As judged from the least squares constants, the estimated response from fixing the H^c allele in the two breeds would be to increase litter size by about one-half to one extra pig. This would be equivalent to about five to 10 generations of selection for litter size. However, if the H system does influence litter size, natural selection should already have fixed the H^c allele unless it is opposed by different selection forces at other times in the life cycle. The small effect of the H^c allele in decreasing weight for age seems unlikely to be large enough to balance natural selection for litter size.

In studies of association between blood groups and productive traits, often one or two factors or systems appear to have useful effects on the traits being studied. However, in subsequent analyses, such effects are often unconfirmed or even contradicted. For example, Schrape (1966) did not confirm the earlier findings of Baltzer (1964) and Rausch *et al.* (1967) in a study with cattle found effects of the BO_1Y_1D' factor on fat percentage to be opposite in sign to those reported by Neimann-Sørensen and Robertson (1961). Therefore, the effects may be unreliable bases for selection, misdirecting the selection effort and decreasing the rate of improvement (Smith, 1967). The present results on the H system will need to be confirmed by other studies, especially since smaller effects and a decrease in the percent of the variance explained were found using the restricted model (3). On the other hand, improvement of litter size by direct selection is likely to be slow and the possibility of quick gains through the H system may be worth the risk of failure.

Summary

Twelve blood and four serum systems were studied to determine their relationship with other traits in two breeds of pigs. Data were from 16,000 pigs in 2,000 litters involving 429 sires. Thirteen percent of 300 F-tests from within group least squares analyses of variance, indicated significant ($P \leq 0.05$) relationships among blood and serum systems and the traits studied. Least squares estimates for phenotypes were not consistent between breeds, although some similarities were noted, and the effects found did not confirm the results reported in other studies with pigs. A major and consistent effect of alleles at the H system on reproductive performance was found. Less than 2% of the variance in the productive traits was accounted for by the systems collectively but from 0 to 12% was explained in the reproductive traits.

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42. DEVELOPMENT OF A PIG SIRE LINE BY SELECTION, WITH IMMIGRATION

J. W. B. King and C. Smith, *A.R.C. Animal Breeding Research Organisation, Edinburgh 9.*

A specialised sire line of pigs, selected primarily for low backfat thickness, has been developed. The foundation stock was from a four-way cross of British breeds. In subsequent generations immigration was allowed into the line on the basis of carcass merit. Immigrants were mated to animals in the line and their progeny competed for selection with contemporary animals. Selection was made at around 180 lb live weight on ultrasonic fat measurements, the intensity of selection being about 1 in 8 for males and 1 in 3 for females.

Backfat thickness decreased phenotypically by 12 mm (about 4 standard deviations) in five generations (years) but then only decreased slightly in the last two years. Comparisons were made with Large White pigs at the Stirling Testing Station in 1967. These showed that the average backfat in the sire line was 3–4 mm less than in Large Whites.

The contribution of different breeds at present is approximately: Large White 46%, Landrace 21%, Wessex 3%, Tamworth 2%, Lacombe 3%, Hampshire 9%, and Pietrain 16%. The line is being continued, with further immigration, but selection on feed efficiency has been included.

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OPTIMUM SELECTION PROCEDURES IN ANIMAL BREEDING

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SUMMARY

A simple expression relating the standardized selection differential (i) to the intensity of selection (p) is given by

$$i \simeq 0{\cdot}8 + 0{\cdot}41 \ln (R-1)$$

where R equals $1/p$. This linear expression may allow simpler solutions to some optimization problems in selection than does the conventional formula for selection differential on truncation of the normal curve.

Using the expression, formulae for the maximum *immediate* response and optimum selection intensity in mass selection have been developed, taking account of the loss in performance through inbreeding. These formulae were used to study the effect on response of the total number of animals tested. The maximum response over a specified period of time, allowing for the loss in genetic variance from inbreeding, has also been considered. The optimum intensity of selection may then be well below that necessary for the maximum immediate response.

INTRODUCTION

IN designing and comparing animal breeding plans, the optimum selection procedure for each plan is often required. Genetic response is usually taken as a function of the selection differential achieved and of the accuracy of selection (Lush, 1945). This paper presents an empirical linear relation between the intensity of selection and the selection differential and demonstrates the use of the expression in several selection problems.

SELECTION DIFFERENTIALS

Assuming truncation selection in a normal distribution, the selection differential (i), in standard units, is the ordinate (z) at the truncation point (x) divided by the proportion (p) selected. Values of this quantity are available in many statistical texts and papers and are graphed in Figure 1a, plotting

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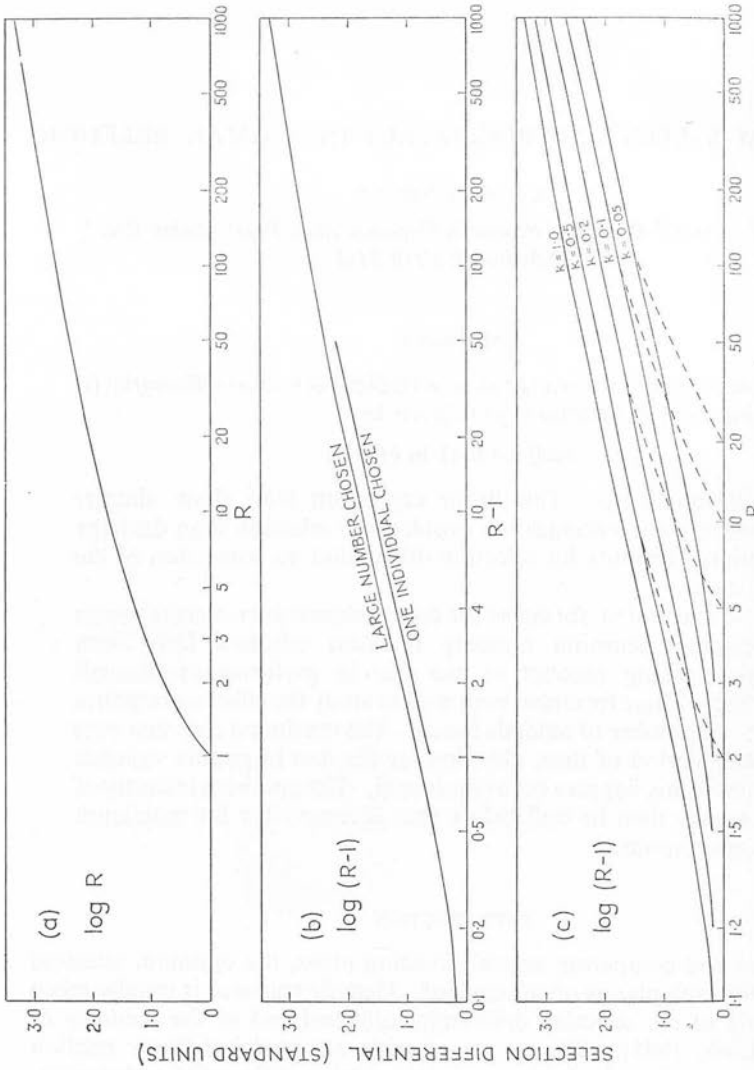

FIGURE 1. *Selection differentials* for $\left(p = \frac{1}{R}\right)$ on (a) a $\log_{10} R$ scale (b) on a $\log_{10}(R-1)$ scale, and (c) from

the selection differential against the logarithm of R, where R equals $1/p$ This graph can be made linear (Figure 1b) over a large part of the range in R by changing the scale of the abscissa to log $R-1$. The empirical relationship is then:

$$i \simeq 0{\cdot}8+0{\cdot}94 \log (R-1)$$
$$\simeq 0{\cdot}8+0{\cdot}41 \ln (R-1) \quad (1)$$

A good linear relationship holds over a range of selection intensity from 1 in 1·5, ($p = 0{\cdot}67$) to 1 in 200 ($p = 0{\cdot}005$), with errors of less than 5% of the tabular values of (i). The expression (1) overestimates the selection differentials at very intense levels of selection, and underestimates them at very low intensities of selection ($p > 0{\cdot}67$).

The advantage of expression (1) in optimization work is that the algebraic differential ($di/dR = 0{\cdot}41/(R-1)$) is simpler than the conventional form for (i), ($di/dp = -(i-x)/p$). It is also simpler than if p were used in expression (1), ($di/dp = -0{\cdot}41/p(1-p)$). Thus use of R and expression (1) may lead to simpler algebraic solutions to optimization problems in selection than do the other two forms.

Approximate solutions provided by expression (1) may be sufficient for the purpose of evaluating different selection schemes. In fact, once the general area of the solution is determined, a more accurate empirical equation for that area can be derived and a more precise solution obtained.

APPLICATION

As an example of the use of expression (1) in a specific animal breeding problem, the optimum balance of the two sexes in testing and selection is considered for mass selection.

With a fixed number T of testing places available, there will be some optimum allocation of places between males and females and some optimum selection intensity in each sex. If the facilities are very limited only a proportion of males required for breeding may be tested and selected (Case 1), the remainder being chosen from untested males. As testing facilities increase all males will be tested and a proportion of the females required for breeding will also be tested (Case 2). Finally, if testing facilities are large all males and all females required for breeding will be tested (Case 3).

Let the following symbols represent the testing and selection situation:

	Males	Females
Number required for breeding	s	sd
Number selected for breeding	m	f
Proportion selected among those tested	$1/R_1$	$1/R_2$
Number tested	mR_1	fR_2

Case 1. If testing facilities are very limited, males will have priority in testing and it will be better to use untested males than to use tested males which are below average. The number tested (T) then equals mR_1 and the response to mass selection is:

$$\tfrac{1}{2}h^2\sigma\frac{m}{s}[0{\cdot}8+0{\cdot}41 \ln(R_1-1)]$$

FIGURE 1. *Selection differentials for* $\left(p = \frac{1}{R}\right)$ on (a) a $\log_{10} R$ scale (b) on a $\log_{10}(R-1)$ scale, and (c) from [illegible]

SELECTION INTENSITY ($p = 1/R$)

This can be shown to be a maximum when the number selected for breeding m is half the number tested T. This result holds until m exceeds s, the number required for breeding, when Case 2 applies.

Case 2. All males required for breeding will now be tested ($m = s$) and a proportion of the females will also be tested and selected, so that $T = sR_1 + fR_2$. The response to mass selection is then:

$$\tfrac{1}{2}h^2\sigma\left[0{\cdot}8+0{\cdot}41\ \ln(R_1-1)+\frac{f}{sd}\,(0{\cdot}8+0{\cdot}41\ \ln(R_2-1))\right]$$

R_2 can be expressed in terms of R_1 and f, the other two unknowns, and substituted in the above expression. Differentiating with respect to R_1 and to f and setting the partials equal to zero gives the simultaneous equations:

$$(R_1-1)/d = (T-sR_1-f)/f \qquad (2)$$

$$\ln[(T-sR_1-f)/f] = (T-sR_1)/(T-sR_1-f)-0{\cdot}8/0{\cdot}41 \qquad (3)$$

Substituting (2) in (3), solving for f and re-substituting in (2) gives:

$$d/(R_1-1)+\ln[d/(R_1-1)] \simeq 1$$

so that $$d/(R_1-1) \simeq 1, \text{ or } R_1 \simeq d+1.$$

That is, as testing facilities (T) increase, the selection intensity in males will increase from 1 in 2 (Case 1) until it becomes 1 in $(d+1)$ and reaches a plateau. This is because further responses in males are then less than the responses from testing a proportion of the females required for breeding. At this stage, females will start to be tested, selecting them at an intensity of 1 in 2. This state of affairs continues as T increases, testing $T-s(d+1)$ females, until all females required for breeding can be selected. When this level is reached the proportion of the testing places allocated to males will be $(d+1)/(3d+1)$. Further testing of males may now become worthwhile and Case 3 applies.

Case 3. All males and all females required for breeding are now tested so that $T = sR_1 + sdR_2$. The expected response can be expressed as before and maximized, whence the solution

$$R_1 = \tfrac{1}{2}[T/s-(d-1)]$$

is obtained. The intensities of selection in both males and females will now increase as T increases. The proportion of testing places allocated to males will be $\frac{1}{2}-s(d-1)/T$. As T becomes large relative to s and d the optimum allocation to males will tend to one half and the selection intensity in males $(2s/T)$ will be d times as intense as in females $(2ds/T)$.

An example of the application of these results is given in Figure 2 for the situation where 10 males (s) and 50 females (sd) are required for breeding. When less than 60 test places $[s(d+1)]$ are available, only males will be tested. When the number of test places available is between 60 and 160 $[s(3d+1)]$ the intensity of selection in males will be 1 in $d+1$, and some females will be tested and 1 in 2 selected for breeding. The proportion of test places allocated to males thus falls and reaches a minimum of 0·375 if 160 places are available. As more test places over 160 become available the selection

intensity in both males and females increases and the proportion of places allocated to males gradually increases again towards one half. The graph for the expected genetic response, also shown in Figure 2, is fairly smooth and does not reflect the underlying changes in the allocation of testing places between the sexes.

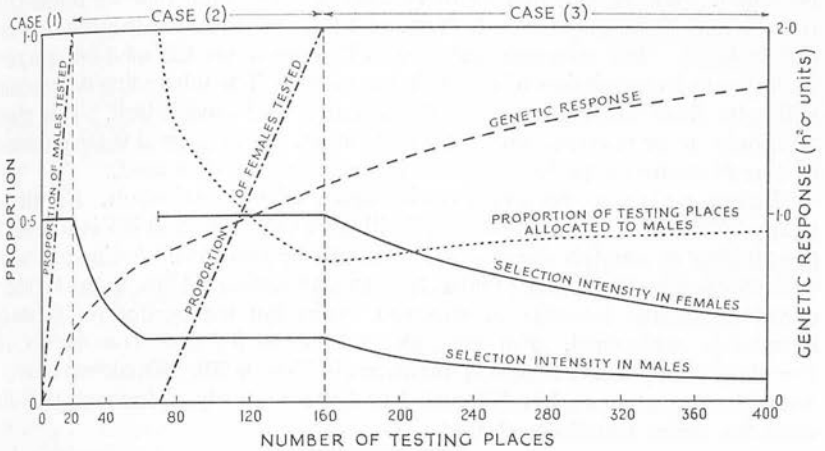

FIGURE 2. Balance of sexes in testing: allocation of test places, proportion tested and selection intensity for each sex, and the overall genetic response [10 males (s) and 50 females (sd) required].

OPTIMUM SELECTION PROCEDURES

Three related problems of general interest in selection are now studied using expression (1). These are (i) the optimum selection intensity for maximum *immediate* response, (ii) the effect of the number of animals tested on response and (iii) the maximization of response over a specified period of time. Allowance is made for the loss in performance on inbreeding and in (iii) the loss of genetic variation due to inbreeding is also considered. However, any additional loss of genetic variation from selection is not considered in these studies.

(i) *Maximum immediate response*

In any breeding plan the response will be proportional to the selection differentials achieved. However, with more intense selection fewer animals are retained for breeding, thereby reducing the effective breeding size of the line and increasing the rate of inbreeding. Extra gains from intense selection may thus be offset by greater losses in performance due to inbreeding. For maximum immediate response there will thus be an optimum intensity of selection and this will vary as the total number of animals tested (T) changes. The optimum may be determined if a linear reduction of performance on inbreeding is assumed. For mass selection in males, with T tested and T/R selected, the rate of inbreeding is approximately $R/8T$ (Lush, 1945). The net gain with a selection intensity (p), equivalent to $1/R$, is then:

$$\tfrac{1}{2}h^2\sigma[0{\cdot}8+0{\cdot}41\ \ln\ (R-1)]-D.R/8T \qquad (4)$$

where D is the change in performance per unit of inbreeding (F).

The response will be a maximum when:

$$\left(\frac{1}{p}-1\right) = (R-1) = 0{\cdot}41.\tfrac{1}{2}h^2\sigma.\frac{8T}{D} \qquad (5)$$

Thus the optimum selection intensity and maximum immediate response can be found. Selection should be more intense if the total number tested (T) is large and if the heritability is high, and less intense if the inbreeding loss (D) is large. The selection response will depend on the additive genetic variation and covariation of the trait concerned. The inbreeding depression will arise from non-additive genetic variation and covariation. This may refer only to the selected (and correlated) traits, but in general the depression of overall economic performance on inbreeding should be used.

Equation (5) provides an interesting and useful general result. For given values of h^2 and D, the term $(R-1)/T$ will be constant, so that if R is not small the number of animals selected T/R will also be constant. A similar result was obtained by Robertson (1960a) for progeny testing. Thus, as the number tested varies, the intensity of selection varies but the number of animals selected is unchanged. For example, with $h^2 = 0{\cdot}5$ and $D = 4\sigma$ (2σ at $F = 0{\cdot}5$), the optimum selection intensities if 1000 or 200 animals were tested would be *equivalent* to 1 in 200 and 1 in 40 respectively. However, in both cases five males would be selected.

(ii) *Number tested and response*

The formula for optimum selection intensity in mass selection can be used to study the effect on *immediate* response of varying the number of animals tested. The changes in selection differential, in inbreeding loss and in net selection response are examined in turn.

If instead of testing T animals, a proportion k of T are tested then from expression (5) above,

$$(R_k-1) = k(R-1)$$

where the new optimum selection intensity (p_k) is equivalent to $1/R_k$. The corresponding selection differentials for different values of k can be read off Figure 1b and are shown in Figure 1c. These differ from the selection differentials (dotted lines), which would result if no change was made in the number of animals selected (same level of inbreeding), only when R or k are small. The converse of these results applies, of course, for proportional increases in the number of animals tested.

The loss in performance through inbreeding for kT animals tested becomes [on substituting for D/T using equation (5)]:

$$\tfrac{1}{2}h^2\sigma(0{\cdot}41)\left(1+\frac{1}{k(R-1)}\right)$$

a constant amount and a term depending on k.

Substituting for D, from expression (5), the response with kT tested *relative* to that for T tested is:

$$1+\frac{\ln k+[(k-1)/k(R-1)]}{1+\ln(R-1)-[1/(R-1)]} \qquad (6)$$

This expression could also be given in terms of T and D, but the form is less concise than with R. As before, the converse of these results applies for

proportional increases in the number of animals tested. Values of the full expression (6) are given in Table 1, and the expected responses are shown in Figure 3. The net responses are less than indicated by the selection differential graphs (Figure 1) since the latter do not include a term for inbreeding loss.

TABLE 1

Efficiency of selection if the number tested is a proportion (k) of total number (T) possible

Original optimum intensity of selection with (T) tested	Proportion (k) tested							
	0·5		0·2		0·1		0·05	
1 in 5	56†	(69)‡	—		—		—	
1 in 10	74	(80)	33	(45)	—		—	
1 in 20	81	(85)	53	(62)	29	(39)	—	
1 in 50	85	(89)	65	(73)	49	(58)	30	(40)
1 in 100	87	(91)	70	(77)	57	(66)	43	(52)
1 in 200	89	(92)	74	(81)	63	(71)	51	(61)
1 in 500	90	(93)	78	(84)	68	(76)	58	(68)
1 in 1000	91	(94)	80	(86)	71	(79)	62	(72)

† Evaluation of expression (6) in text. (Note: for increases in number tested, $k>1$, efficiency of selection is less than reciprocals of tabulated values.)
‡ Maximum efficiency, ignoring inbreeding loss.

The effect on response of changing the number of animals tested depends greatly on the initial optimum intensity of selection. If this is high the numbers tested may be reduced without great losses in response. But if the numbers tested are reduced too far, or if the initial optimum intensity was low, the

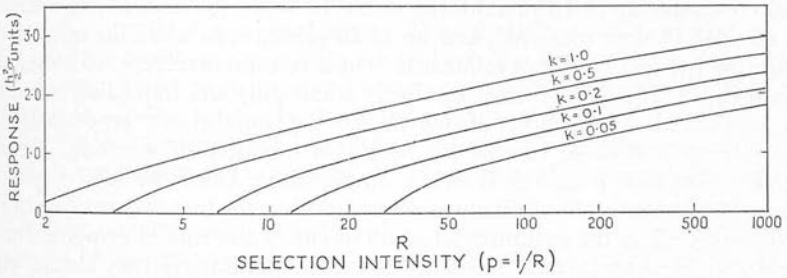

FIGURE 3. *Response* from optimum selection $\left(p = \frac{1}{R}\right)$ when T animals are tested, compared with those when only a proportion (k) of T are tested.

responses may fall off substantially. Later on, expression (6) is also used to examine the effects of partitioning a set of testing facilities among several different lines.

(iii) *Cumulative response*

An important deficiency of the above sections is that they deal only with immediate response and ignore the losses in genetic variation following selection and from inbreeding. In fact few authors have considered these

effects in their work on optimum testing and selection procedures. The losses in genetic variation are cumulative over time, so that the net response from selection will decrease in each successive generation. There is thus likely to be an optimum selection intensity which will maximize the total response *up to some specified time*.

The genetic variance within lines following inbreeding is approximately $(1-F)h^2\sigma^2$, where F is the inbreeding coefficient. The effect of selection on the genetic variation of a character depends on the number of loci involved, on the effects and frequencies of their alleles and on linkage, and is difficult to formalize. The treatment here is thus restricted to quantitative characters controlled by a large number of loci so that changes in gene frequency brought about by selection will have little effect on the genetic variance. Any change in phenotypic variance is also ignored. With these restrictions, the total response (for mass selection in males) up to the gth generation can be written as:

$$g\ \tfrac{1}{2}h^2\sigma\ [0{\cdot}8+0{\cdot}41\ \ln(R-1)]\left[1-\frac{g-1}{2}\cdot\frac{R}{8T}\right]-\left[g\cdot\frac{D\,.\,R}{8T}\right]$$

where the terms represent the selection differential, the cumulative loss of genetic variance and the loss in performance due to inbreeding. Differentiating with respect to R, setting the result to zero and simplifying gives the equation:

$$\frac{1}{(R-1)}\left[\frac{16\,.\,T}{(g-1)}-1\right]-\ln(R-1)\simeq\frac{10\ D}{(g-1)h^2\sigma}+3$$

The value of $R-1$ which satisfies this equation, and maximizes the total response over g generations, can easily be found using ln tables. Taking the case considered earlier ($T = 1000$, $D = 4\sigma$, and $h^2 = 0{\cdot}5$), the maximum total response up to 10 generations would be when the intensity of selection is 1 in 110 (9 sires retained), and up to 20 generations when the intensity of selection is 1 in 75 (14 sires retained). These results correspond to a selection intensity of 1 in 200 (5 sires retained) when only the immediate response is considered. The effect of increasing the number of generations (g) considered is thus to reduce the optimum intensity of selection, but the relation between g and R is not a simple one. Since the loss of genetic variation from selection is likely to be greater than the loss of genetic variation from inbreeding, the optimum selection intensity and rate of response would probably be even further reduced. Since the parameters may change with selection, the value of the optimization procedure may fall as the number of generations (g) is increased. For maximum response over a very long period of time, the optimum selection intensity is known to be one in two (Robertson 1960b).

DISCUSSION

The empirical linear expression for the selection differential appears to offer a useful simplification in the solution of several selection problems. In this paper, most of the problems studied have referred to the simple case of mass selection in males. With indirect or family selection, or with index selection, the solutions will be more complex, but expression (1) may still allow some simplification. Of course empirical results can be obtained by

evaluating the complex expressions by computer, for ranges of relevant variables in selection. Indeed the response surfaces may be more useful and informative than are the optimum points themselves. The value of the formulae and solutions given here is to provide some basis for discussion of selection problems and to indicate both the critical variables and the general form of the results.

Selection for maximum immediate response is likely to require more intense levels of selection than are common in livestock breeding schemes at present. There are several reasons for this. In practice, there may be biological or practical limits on selection intensity, for example if reproductive rate is low. Short-term responses are important in competition among stocks and among breeders, but they are achieved at the expense of further responses in the long term. Animal breeders seem to have rationalized this dilemma by empirically setting levels of inbreeding which are tolerable and will permit a balance between immediate and long-term gains. This may correspond to the result found for immediate response, that a constant number of animals should be selected, irrespective of the number tested. However, it is important to establish whether the empirical levels set on inbreeding are near optimum and to study how the optimum levels are affected by the intended length of the breeding programme.

Both the loss in performance and the loss of genetic variation on inbreeding will be involved in determining the response, but only one may be critical. For example, if the loss in performance (overall merit) were recouped on line crossing, inbreeding losses within lines could be ignored and very intense selection used. However, the loss in genetic variation due to rapid inbreeding would then become important and more moderate levels of selection would be indicated. The possibility of selecting several sub-lines to take advantage of differential rates of response among lines (and by crossing, avoid losses from inbreeding) is sometimes advocated. This may be useful, but only in the short term. The selection intensity and response in s sub-lines could either be reduced to keep the same rate of inbreeding (F), or maintained as in a large line so increasing the rate of inbreeding within each sub-line to sF. In the latter case, losses in genetic variance may reduce further responses, while new lines formed by crossing the original s sub-lines would have the same level of inbreeding (sF/s) as in a single large line.

In selection there may be different economic goals or different environments to be accommodated. Will it be more efficient to select individual sub-lines to satisfy individual requirements or to select in a single line on an index combining the various sets of requirements and to rely on the correlated responses? Expression (6) provides some guide to a solution of this problem. Assuming that the heritabilities of the different requirements are equal, selection in a single line will be the more efficient procedure when the average genetic correlation ($\bar{r}_G$) of the index with the various sets of requirements is greater than expression (6) (evaluated in Table 1). As the selection intensity ($1/R$) possible in a single line decreases and the number of sub-lines $\left(s = \frac{1}{k}\right)$ required increases, so the critical value of $\bar{r}_G$ also decreases. Of course, when the genetic correlations among sets of requirements are low, zero or negative, then there is no alternative to distinct sub-lines, although the rate of response in each will then be lower.

ACKNOWLEDGEMENT

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Heritability of liability and concordance in monozygous twins

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Falconer (1965) presented a method of measuring the correlation between relatives for a disease from data on the incidences of the disease in the general population and among relatives of affected individuals. The model assumes an underlying continuous liability to a disease, the liability being made up of many genetic and environmental factors and thus normally distributed. The disease becomes manifest if an individual's liability exceeds a critical threshold level. The derived correlation between relatives may be used, in the absence or elimination of common familial environmental factors, to provide an estimate of the heritability of liability to the disease.

Two sources of bias remain in Falconer's (1965) method of estimation. These arise because affected individuals (those exceeding the threshold) form a truncated group with a skewed distribution. Thus the variance of liability among their relatives may be reduced and the distribution of relatives may be skewed. Falconer (1965) suggested that these biases would be small, but pointed out (Falconer, 1967) that the skewness could bias estimates of heritability of liability in monozygotic (MZ) twins, giving estimates which are too high.

Edwards (1969) overcame the difficulties of skewness and reduced variance by using tetrachoric functions for bivariate normal distributions. He presented a graph which relates population incidence and incidence in relatives of affected individuals for *any* correlation between relatives in liability. His results show that Falconer's original method gives estimates of heritability which are about one-tenth too low. In this paper Edwards's results are confirmed and extended, using a different approach to the problem. Then the genetic interpretation of concordance rates in MZ twins is examined in the light of the theoretical results obtained.

METHODS

The problems of skewness and of reduced variance, inherent in Falconer's method, arise because a truncated (affected) part of the population is chosen. These disappear when the population is considered as a whole.

The model used assumes a normally distributed liability and absence of familial environmental factors, so that the correlation (r) in liability between relatives equals Rh^2, the genetic relationship multiplied by the heritability of liability. The method of solution was to generate an ordered series of genetic classes from a normal distribution. Then from each class, and for different levels of incidence and heritability, the proportion of relatives exceeding the threshold value was estimated. Pooling the proportions for all genetic classes, a set of graphs or tables was derived giving the correlation (or heritability) corresponding to any combination of incidences in the population and in relatives of affected individuals.

The details of this method are shown in Table 1 (p. 88). The incidence (q_P) in the population specifies the threshold point (T). Given the heritability (h^2), the genetic variance and distribution

of liability in the population are known. The frequency (f_i) of the ith genetic class, its mean deviation ($x_i h$) and the mean deviation ($Rx_i h$) of its relatives from the original mean and so from the threshold point (T) can be found. Then taking account of the respective residual variances, the proportions of each genetic class (P_i), and of relatives (P'_i), exceeding the threshold can be estimated. Combining the proportions for all genetic classes, the incidence (q_R) in relatives of affected individuals is obtained.

The various calculations were done by computer using three subroutines to evaluate functions of the normal curve: (1) to get the mean and frequency in each of 40 equally spaced genetic classes (from -4 to $+4$ standard deviation units), (2) to calculate the deviate (x) given the incidence (q), using a complex algorithm from Hastings (1955), and (3) to find the value of q given x, by accumulating the frequency of classes exceeding x. A wide range of values for incidence, heritability and genetic relationship was used.

RESULTS

The results confirm those of Edwards (1969). They are plotted in Fig. 1, to correspond in form with Falconer's original graphs and to allow more accurate readings than are possible from Edwards's paper. The equivalence with Edwards's graph shows that the results depend on the correlation (r) between relatives in liability. This was confirmed in that the same results were always obtained for a given value of r, equal to Rh^2, for different combinations of R and h^2. In the absence of environmental similarities among relatives, the graphs in Fig. 1 are thus general for all coefficients of relationship (R) by choosing the line for r equal to Rh^2. However, the composition of the genetic variance measured by the heritability will differ for different relatives; including all the additive variance but differing proportions of the dominance and epistatic variance for different genetic relationships (e.g. Falconer, 1960).

Incidence in relatives may, by sampling, be less than the population incidence. This would give rise to negative estimates of heritability of liability as shown in Fig. 1. These should be included when pooling estimates, since taking only positive estimates will bias the overall result.

The variance of estimates of the correlation (or heritability) will depend largely on the variance of the estimate of incidence in relatives. This variance, $V(\log_{10} q_R)$, is $0{\cdot}189/A$ on the $\log_{10}$ scale of Fig. 1, where A is the number of affected relatives. Thus the variance of a correlation estimate can also be read simply from Fig. 1. For example, with five affected relatives, the standard error of $\log_{10} q_R$ is $\sqrt{(0{\cdot}189/5)} = 0{\cdot}194$. This is equivalent to 0·95 cm. on the ordinate of Fig. 1, since 4·9 cm. cover one log unit. At $q_P = 0{\cdot}1\,\%$, $1{\cdot}0\,\%$ and $10\,\%$ respectively the standard error of a heritability estimate of 0·5 from first-degree relatives would be, from Fig. 1, approximately 0·10, 0·16 and 0·32, corresponding with the values obtained by Falconer's (1965) formulae.

The simple geometrical pattern of the lines in Fig. 1 provides a good algebraic approximation (to within 5 %) of the values of the correlation (r), namely:

$$\tan\left(\frac{\pi}{4}(1-r)(1+r^5)\right) = \log q_R/\log q_P$$

and solving for r. The fifth-degree term can be omitted unless r exceeds 0·5; that is, when the situation refers to MZ twins for diseases with high heritability.

Another useful expression can adjust the tabulated correlations (or heritabilities) if the patients represent one population (A) and the relatives are drawn from another population (B

for example, with regard to sex or age. From Fig. 1 an estimate (r_t) is obtained, using the population incidence for B and the incidence of relatives for B. The adjusted correlation is then simply

$$r_t \left\{ \frac{(\log q_{PB}) - 1}{(\log q_{PA}) - 1} \right\}$$

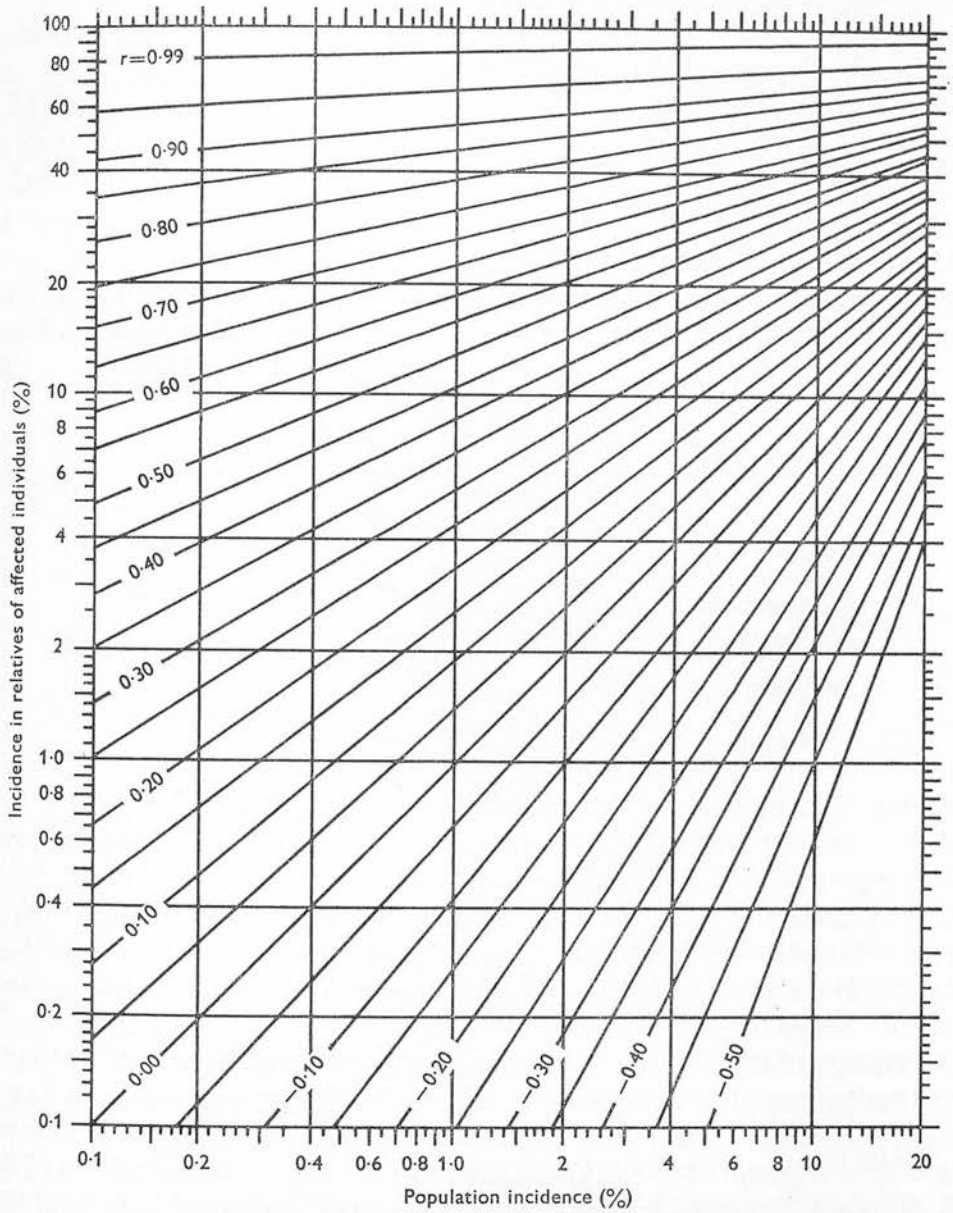

Fig. 1. Graph of the correlation (r) in liability between relatives, given the population incidence and the incidence in relatives of affected individuals. (In the absence of environmental similarities between relatives r equals Rh^2, the coefficient of relationship (R) multiplied by the heritability of liability (h^2)).

To check on the accuracy of this expression, the expected incidence was calculated for relatives in B of patients in A, using the same methods as before and merely changing the threshold level for relatives (Table 1) to that for incidence in B. The expression proved very accurate and could

adjust the correlation (or heritability) for large (up to 100-fold) differences in incidence to within 5 % of the true value. For example, if $R = 0{\cdot}5$, $h^2 = 0{\cdot}5$, $q_{PA} = 0{\cdot}1\,\%$, $q_{PB} = 1{\cdot}0\,\%$ or 10 %, then q_{RB} was found by computer to be 6·2 % and 32·5 %, respectively, giving the corresponding tabulated heritability values of 0·65 and 1·00. Using the above expression, the adjusted heritabilities became 0·49 and 0·50 respectively.

The results in Fig. 1 also apply to MZ twins, if common environmental effects are absent or can be eliminated. The incidence in co-twins is usually expressed as a concordance rate (the proportion of co-twins affected for each twin independently ascertained) and can be read off Fig. 1 for different levels of heritability and population incidence. To bring out a striking feature of the results, they are shown in another form in Fig. 2. In the absence of environmental similarities, concordance rates in MZ twins will not be expected to be high unless the heritability is very high (or the population incidence is very high). For example, in a disease with incidence of 1 % in the general population, the expected concordance rates in MZ twins would only be about 13 % if the heritability was 50 % or about 37 % if the heritability was 80 %. Thus a low

Table 1. *Parameters used in the evaluation of incidence in relatives of affected individuals*

(Population incidence, q_P; threshold, T; heritability, h^2; genetic relationship, R.)

Genetic class (i)	Individuals	Relatives
Genetic mean	$x_i h$	$Rx_i h$
Frequency	f_i	f_i
Residual variance	$1-h^2$	$1-R^2h^2$
Mean deviation from the threshold	$\dfrac{T-x_i h}{\sqrt{(1-h^2)}}$	$\dfrac{T-Rx_i h}{\sqrt{(1-R^2h^2)}}$
Proportion exceeding the threshold	P_i	P_i'
Incidence in relatives of affected individuals	$\sum_i f_i P_i P_i' / \sum_i f_i P_i$	

concordance rate in MZ twins cannot be taken to prove that the heritability is low. High MZ concordance rates may indicate either a very high heritability, or that common environmental factors are important. These alternatives may be resolved, as in conventional twin analysis (e.g. Kempthorne & Osborne, 1961), by comparing estimates of correlations in liability for MZ twins, for dizygotic twins (DZ) and among full-sibs. For example, the expression $2(r_{MZ}-r_{DZ}$ estimates the heritability, while the term $(2r_{DZ}-r_{MZ})$ estimates the importance of common environmental effects in twins.

A good example of the dilemma posed by finding low MZ concordance rates but high heritability estimates from other relatives is given by clubfoot (talipes equinovarus). Ching, Chung & Nemechek (1969) concluded that inheritance was multifactorial with a heritability of liability of 0·68. Wynne-Davies (1970) found an estimate of 0·60 for heritability of clubfoot using British data. However, they quote, as anomalous with their results, data of Idelberger (1939) on 174 twin pairs (40 MZ and 134 DZ) with at least one member of the pair having clubfoot. The concordance rates were 33 % for MZ and 3 % of DZ pairs. Taking the population incidence as 0·12 % in Caucasians, estimates of heritability of liability from Idelberger's data are:

from MZ	$0{\cdot}83 \pm 0{\cdot}06$,
from DZ	$0{\cdot}78 \pm 0{\cdot}16$,
from $2(r_{MZ}-r_{DZ})$	$0{\cdot}88 \pm 0{\cdot}34$.

Thus the MZ concordance rate is not too low and anomalous with the other data but is as expected (or rather high) for multifactorial inheritance. A similar resolution of apparently conflicting data from twins and from other relatives may be possible for other diseases; for example, for schizophrenia (Gottesman & Shields, 1967).

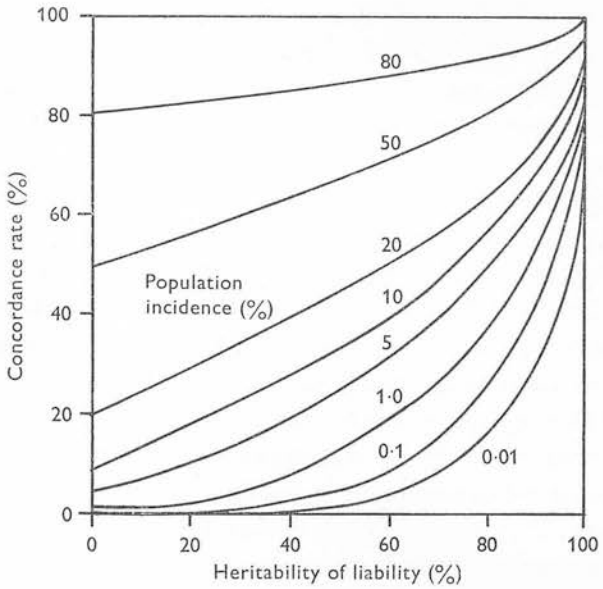

Fig. 2. Expected concordance rate in monozygotic (MZ) twins given the population incidence and the heritability of liability.

DISCUSSION

In comparison with Fig. 1, Falconer's (1965) graph and formulae underestimate the correlation between relatives by about 10 % of the true estimate. Thus, in absolute units, the bias is only important when the correlation is high. The anomalous situation of overestimation of heritability in MZ twins, discussed by Falconer (1967), arises only when the correlation between MZ twins is very high (over 0·9). Falconer's (1965) original method may still be useful in many analyses where the present methods and results are difficult to apply—for example, in complex situations involving degree of severity or onset age or any partition of the affected group by some measure of liability.

The abrupt threshold model has been criticized as unrealistic and Edwards (1969) has considered an alternative of attaching a risk function to a normally distributed liability. The empirical risk function used, however, tends to infinity at the limit rather than to unity. The present approach shows how the threshold model implies a normally distributed *genetic* liability, with a cumulative normal risk function, determined by the population incidence (setting the threshold) and by the heritability (determining the residual variance in a genetic class) of disease. The abrupt threshold is thus conceptual rather than real and may be avoided by redefining the variance and risk function.

The improved estimates of heritability of liability should not obscure possible deficiencies of the model in summarizing data on population and familial incidences of a disease. These have been well discussed by Edwards (1969) and others. The method appears to be robust in practice,

and reasonable estimates of heritability have been obtained for several diseases (Carter, 1969). It thus provides a useful tool in understanding and utilizing information on multifactorial disease. However, because its application is simple, there is some danger that the method may be used uncritically and indiscriminately. For example, few authors have tried to estimate or eliminate the effects of environmental similarities among relatives, and these may be important.

A feature of Falconer's (1965) model is that it is descriptive rather than analytical. By combining data on many families genetic heterogeneity may be masked rather than elucidated. However, it may be possible to deduce the underlying genetic basis of a disease—for example, by comparing heritability estimates from different kinds of relatives. Thus, if heritability estimates were larger from sib data than from parent or offspring data, then recessive alleles at one or several loci might be indicated. Some resolution of heterogeneity may also be possible by partitioning a condition into different classes by some criterion. A measure of effectiveness of a partition is given by the genetic correlation between classes, which tends to zero as distinct classes are identified. The heritability of the combined condition will be less (not greater as Edwards (1969) suggests) than the weighted average of the heritabilities in the separate classes. The reverse applies if the partition does not separate different genetic classes within a condition.

Morton *et al.* (1970) have examined the additive continuous models of Falconer (1965) and Edwards (1969), incorporating terms for consanguinity. They have also presented a discontinuous 'load' model which takes account of loci with additive effects and also of rare loci with large non-additive effects. They found that the discontinuous model gave a good fit more often than the other two models when tested on several sets of data, which included incidences in different kinds of relatives and in consanguineous marriages for several familial diseases. However, all models gave similar estimates of recurrence risks.

SUMMARY

Results from heritability of liability model of Falconer (1965) have been revised, eliminating two sources of bias. The results have been graphed for convenient usage, and in the absence of environmental similarities among relatives can apply to all kind of relatives. Confidence levels for the heritability (or correlation) estimates can also be read directly off the graph.

The results also apply to concordance rates in MZ twins. They show that, in the absence of environmental similarities, concordance rates for a disease in MZ twins will only be high if the heritability is *very* high. Thus a low concordance rate in MZ twins cannot be taken to prove that genetic factors are not important in the predisposition to a disease.

I am indebted to Dr O. Mayo and Dr D. S. Falconer for constructive criticism and advice in the development of this paper; and to Dr T. Gedde-Dahl for some unpublished results on concordance in twins. The approach used arose during discussion with Dr W. E. Nance.

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Ascertainment and Prevention of Genetic Disease

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Summary: A genetic register system has been developed for the ascertainment and prevention of genetic disease. Its potential value is illustrated with data collected from 478 families with serious genetic disorders which had been seen during the past five years. Of these 249 were referred specifically for genetic counselling, autosomal dominant disorders accounting for the largest group of families with individuals at high risk of becoming affected. Of 717 individuals at high risk of having affected children (or carrier daughters in the case of X-linked recessive disorders), only 101 were referred specifically for counselling. Many were referred only after the birth of an affected child which might otherwise have been prevented. A genetic register system linked to practitioner, hospital, and health department records could be a valuable means of preventing genetic disease.

Introduction

In recent years several investigators have argued the need for some form of genetic disease register (Miller, 1964; Newcombe, 1966; Renwick, 1968; McKusick, 1969; Wertelecki, Lawton, and Gerald, 1969). Most of these reports, however, have been concerned only with identifying affected individuals for either welfare or research purposes. Yet in such families there are likely to be others who are also at risk of becoming affected or of having affected children. Ascertaining and following-up such people are important practical reasons for establishing a genetic disease register.

The potential value of a register system in preventing different types of genetic disease has already been discussed (Smith, 1970). In this department such a register is being developed and is referred to by the acronym "RAPID" (Register for the Ascertainment and Prevention of Inherited Disease). The aim of this report is to illustrate the potential usefulness of a genetic register system in preventing disease by using data on the families of people who have been referred to us during the past five years.

Patients and Methods

All the families studied came from either the Edinburgh or the Manchester regions. Many families were referred specifically for genetic counselling but others were referred for different reasons—for example, research interest, teaching, diagnosis, etc. Some families, mainly with hereditary myopathies, were also traced from hospital and health department records. No attempt has been made to ascertain all cases of genetic disease within a region. This is therefore a family rather than a population study.

Only patients with *serious* hereditary disorders have been included. Those referred for chromosome studies because of abnormalities of sexual development or for advice about consanguinity when there was no family history of a serious hereditary disorder have been excluded. The term "multifactorial inheritance" refers to familial diseases which are possibly due to many genes plus the effects of environment; these include idiopathic epilepsy, schizophrenia, and certain congenital malformations (Carter, 1969).

Pedigree data were usually obtained from the first person in a family to be seen, and this provided most of the information on which the following analyses were based. From the pedigree and the known mode of inheritance risks were calculated for all individuals of (*a*) becoming affected themselves (in late manifesting diseases such as Huntington's chorea) or, if under 40 years of age, of having (*b*) an affected child or (*c*) a carrier daughter in the case of X-linked recessive disorders such as haemophilia and Becker type muscular dystrophy. Risks were calculated by Bayesian methods (Murphy, 1968) based on the family history and relevant biochemical tests when these were indicated (Emery and Morton, 1968). The number of cases which might have been prevented by genetic counselling has also been estimated.

"Preventable cases" have been defined as affected children born in the past 10 years to parents who, a priori, were at high risk of having affected offspring. For example, a boy with an X-linked recessive disorder would be included if his maternal grandfather was affected, because in this situation his mother must be a carrier; but the first child in a family to be affected with an autosomal recessive disorder would not be included.

Details on all subjects at high risk (arbitrarily defined as being greater than 1 in 10) were recorded on cards specially designed for computer storage, analysis, and follow up. Full

Individuals at Risk in Families with Serious Genetic Disorders Referred Specifically for Genetic Counselling (C) or for Other Reasons (O). (Number of Families Given in Parentheses)

	Autosomal Dominant (108)		Autosomal Recessive (93)		X-linked Recessive (87)		Multifactorial (81)		Chromosomal (26)	
	C	O	C	O	C	O	C	O	C	O
At risk of becoming affected	7	238	0	0	0	27	0	8	0	0
At risk of having affected children or carrier daughters in X-linked disorders	28	331	35	11	18	269	18	5	2	0
"Preventable cases" (see text)	12	9	12	1	6	14	2	0	0	0

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details of the register, including operational details and the design of the register cards, will be published later.

Results

Data on 478 families have been collected. In 83 families the disorder in question either proved not to be genetic or the cause was unresolved. No individuals were considered to be at risk in these families. The distribution of the various types of genetic disease (see Table) among the remaining families is not representative of the population as a whole, but partly reflects the department's particular interests—for example, in the X-linked muscular dystrophies.

Of the 478 families, 249 were referred specifically for genetic counselling—50 autosomal dominant, 56 autosomal recessive, 33 X-linked recessive, 61 multifactorial, 22 chromosomal, and 27 in which the disorder was either not genetic or the cause was unresolved.

Individuals at risk of becoming affected themselves mainly concerned autosomal dominant disorders—that is, 245 out of a total of 280 subjects were considered to be at risk. This is mainly because many of these disorders were of late onset and occurred in large families—for example, myotonic dystrophy, Huntington's chorea, and polyposis coli.

Of 717 subjects at risk of having an affected child or of having a carrier daughter (X-linked recessive disorders), autosomal dominant and X-linked disorders accounted for 646. In the case of autosomal dominant disorders many were at risk both of becoming affected and of having affected children.

A total of 56 affected children ("preventable cases") were born to parents who, a priori, were at high risk of having affected offspring. There were a further 94 individuals at high risk of becoming affected, but so far they have shown no signs of the disease.

Discussion

Our results indicate that the main scope for preventing genetic disease lies with the simply inherited disorders, because in general the proportion of individuals at high risk is greater than in the case of multifactorial and chromosomal disorders. Even in simply inherited disorders, however, it will be possible to prevent only a proportion of cases, since some will occur in families in which there has been no previous history of the disease.

Only a relatively small proportion of individuals at risk of having affected children (or carrier daughters in the case of X-linked disorders) were referred specifically for genetic counselling (101 out of a total of 717, or 14%). Many affected children were born to parents who, a priori, were at high risk of having affected children but who had never been counselled and were therefore unaware of the risks. Others were referred for counselling only after the birth of an affected child which might otherwise have been prevented. At present no defined procedure for tracing such individuals exists. Herein lies the value of a genetic register system.

The first step in such a system is the ascertainment of those at risk. This could be achieved through general practitioner, hospital, and health department records linked to a genetic register. The next step is to develop procedures for contacting, through their family doctors, individuals who are found to be at risk. The final step is to provide adequate advice and follow-up for those at risk. The latter could be achieved through a genetic register system. This approach to the prevention of disease could have important implications, both for the individual and for society. Not only would such a register be of value in tracing and following up those at risk of having affected children but it might also be of value in alerting individuals with inherited susceptibilities to drugs and for detecting aid eradicating life-threatening complications of genetic disease, such as intestinal malignancy in polyposis (McKusick, 1969). The main function of such a register system, however, would be to prevent genetic disease.

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CHAPTER 13

ASCERTAINING THOSE AT RISK IN THE PREVENTION AND TREATMENT OF GENETIC DISEASE

CHARLES SMITH

INTRODUCTION

There has been a dramatic change in the pattern of morbidity and mortality in the British population over the last 30 to 50 years: genetic disease has been less affected by advances in medicine and improvements in environment, and has consequently increased in its relative importance as a cause of morbidity and mortality. For example with the decline in neonatal mortality congenital abnormalities, many of which are at least partly genetic in causation, now account for some 20 per cent of infant mortality compared with about 5 per cent at the turn of the century (Carter, 1963). Similarly, control of infectious diseases and the use of drugs and antibiotics have reduced childhood and early adult mortality so that many chronic non-communicable diseases with onset in adult life, such as diabetes and ischaemic heart disease, have become relatively more important, and many of these have some genetic basis.

With the increasing role of preventive medicine in medical care it is worth while to examine what scope there is for ascertaining those at risk in the population in prevention and treatment of genetic disease. In this context the extent and nature of genetic disease are reviewed.

A framework is developed for classifying possible methods of detection and prevention. The value of different methods and routes of ascertainment are then examined and various preventive procedures are discussed. Finally the integration and use of information from different sources are considered.

NATURE AND EXTENT OF GENETIC DISEASE

Various 'types' of genetic disease and their respective frequencies are outlined in Table 1. On the one hand there is a group of conditions which are inherited in a fairly simple and well understood manner. Individually these have low frequencies but they are numerous (McKusick, 1966) and on aggregate they comprise about

TABLE 1
Nature and Extent of Genetic Disease

	Frequency (F) per 1000	*Relative risk in sibs*	*Reference*
Simple inheritance			
Malformations due to a single gene substitution	5	—	Stevenson (1961)
Disorders due to a single gene substitution	8	—	Stevenson (1961)
Chromosomal aberration disorders	4	—	Stevenson (1961)
Haemolytic disease of the newborn	4	—	Stevenson (1961)
Complex inheritance			
Congenital abnormalities	23	5–20	Carter (1965)
Diabetes mellitus	8	3	Simpson (1964)
Renal stone disease	4	6	McGeown (1960)
Simple glaucoma	8	10	Hunt (1965)
Schizophrenia	9	14	Kallman (1953)
Peptic ulcer	39	2	Doll and Buch (1950)
Hypertension and ischaemic heart disease	50	8	Platt (1963); Slack and Evans (1966)

2 per cent of all live births. On the other hand, there are many diseases with a significantly raised familial frequency, but whose inheritance is complex and often ill-understood. The congenital abnormalities and many of the chronic non-communicable diseases with onset in adult life fall into this group. Roberts (1962) has grouped genetic diseases into those with a high risk of recurrence (greater than 1 in 10) and those with a low risk of recurrence (less than 1 in 20) in affected sibships. In general the simply inherited conditions (Table 1) come into this former category, while the remainder fall into the low risk group. Apart from the recurrence risk, the severity of the condition and duration of the disease may also have to be considered.

For the complex genetic diseases familial aggregation is usually measured by the 'relative risk' (k), the ratio of the frequency in relatives of affected individuals to the frequency in the population. Although useful in practice in assessing risks to other family members the relative risk is not a suitable statistic for measuring the importance of heredity in a condition because it depends on the frequency. A more appropriate measure is the 'heritability of liability' (Falconer, 1965) which takes into account the population frequency (F) as well as the relative risk (k). For several of the diseases listed in Table 1, initial estimates of heritability have been moderate to high (Falconer, 1965, 1967; Carter, 1969), indicating that heredity is important in the aetiology of these diseases.

Morton (1967) suggests that many traits and diseases whose inheritance seems complex at present, may each be eventually resolved into a few simple genetic entities, and has presented a method to determine if a few major loci or many loci with small effects are involved.

Relative Importance of Genetic Disease

It is difficult to find figures or criteria by means of which to assess the importance of genetic disease, relative to other diseases. But a rough guide may be had from the proportion of the expenditure on medical care spent as a result of genetic disease. Of the total expenditure in the United Kingdom (£665 million in 1961–62) congenital abnormalities accounted for 0·6 per cent (Office of Health Economics, 1964). This figure compares with about 1 per cent for diabetes, 3 per cent for heart disease and 17 per cent for all mental disease. There seems to be no comparable figure for the simply inherited diseases but, because of their low frequency, they can form only a small part of the cost of disease to society. However

by their nature, they may allow more possibility in prevention than do the more common complex genetic diseases.

ROUTES AND METHODS OF ASCERTAINMENT

The methods of ascertaining, treating and preventing genetic disease depend on many factors such as the nature of the condition, the mode of inheritance and the frequency of occurrence. An attempt is made in *Figure 1* to give a formal structure to the various routes and methods involved and within which particular procedures can be classified. Central to this concept is some form of information

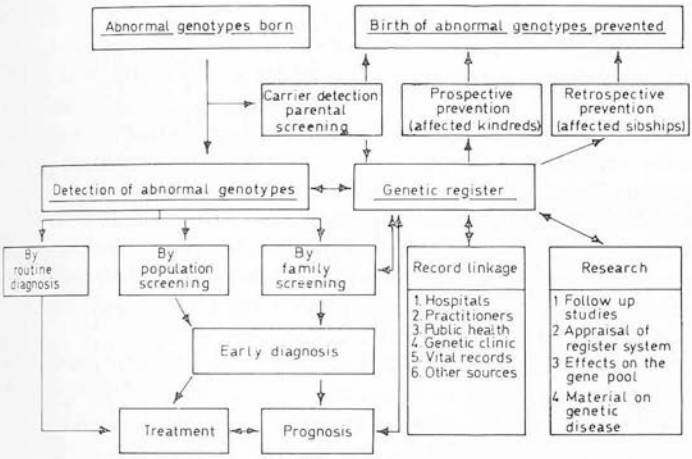

Figure 1. Diagram of routes and methods of ascertainment in prevention and treatment of genetic disease

system (here termed a genetic register) which can store, integrate and *use* the information available.

Logically there are two ways of approaching genetic disease. One is to prevent the birth of abnormal genotypes. The other is through detection and treatment, as a means of alleviating the effects of the disease.

Detection of genetic disease will depend, for the most part, on routine diagnostic procedures, and then treatment (if available) can be applied. For certain conditions early detection and early treatment may improve the prognosis, as in galactosaemia. Then some special screening procedures to detect affected individuals may be initiated,

dealing either with the whole population or with groups at specia risk—for example, sibs of individuals with simple glaucom (Paterson, 1965).

Upon detection of an affected individual, the particular famil and the disease are identified. Use can then be made of this info mation (through a genetic register) to prevent the birth of furth affected individuals in the sibship in which the affected individu occurred (retrospective prevention) and in the rest of the family kindred (prospective prevention). Genetic counselling may b limited to those seeking advice, or efforts may be extended to dete all relatives at risk. Rather than restrict prevention to affecte families, it may be possible for some specific conditions to screen a parents and so detect matings at risk.

Storage, retrieval and integration of family information o genetic disease in a genetic register is essential in an effective, pr ventive system. Individuals and families at risk could then be ful ascertained and monitored, especially during their period at ris Through record linkage, the genetic register could have access useful information from several sources, such as vital record personal health records and hospital records. Through the regist the effectiveness of counselling and preventive procedures could b assessed and the short-term and the long-term effects on society any preventive measures or methods of treatment could also b assessed. Finally the genetic register would be a useful source material in research on genetic disease.

The main concern in this Chapter is to examine the value different methods and routes of ascertaining those affected or at ri from genetic disease, and to estimate how much genetic dise could thereby be prevented or eliminated. In order to do this, set of idealized conditions is assumed, for example that counsell is completely effective, that family size in families at risk is the sa as in the general population, that all cases are reported, that t disease is not heterogeneous, that abnormal genotypes can b detected early and that tests for carriers are available and accura It is unlikely that all these conditions will hold in practice for a particular genetic disease, so that the proportions preventable may less than those given which are therefore *maximum* values.

PREVENTION OF BIRTH OF ABNORMAL GENOTYPES

Prevention of the birth of abnormal genotypes may be eith *prospective* (before an affected child has been born to a parent at ri or *retrospective* (after the birth of an affected child). As defined be

retrospective prevention applies to possible *further* cases in *affected sibships*, and prospective prevention applies to all others—either by preventing possible cases from parents in the rest of the family or by screening all potential parents to detect those at risk. A proportion of cases will be due to new mutations in the affected individuals and cannot be prevented by these methods.

Retrospective Prevention

After the birth of a child with a condition which has a high recurrence risk, parents may be counselled to have no further children (unless detection *in utero* and selective abortion are possible). What proportion of all affected cases could then be prevented? Fraser and Motulsky (1969) have shown, for an autosomal recessive condition, that if parents with one affected child had no further children, the reduction in frequency would be

$$1 - \Sigma_n \, s_n \frac{1}{n} \; \Sigma_{i=1}^{n} \, (1-A)^{i-1}$$

where (s_n) is the frequency of family size (n) and (A) is the probability that the next child would be affected. The larger the family size, the greater is the value of retrospective prevention. A guide to the distribution of *completed* family size has been taken from the 1961 British Census for mothers in the 40 to 49 year age group:

Number of children	1	2	3	4	5	6	7	7+
Frequency	·30	·35	·18	·08	·04	·02	·01	·02

Using these figures, the *maximum* proportion of cases which could be avoided by retrospective prevention would be about 0·15 for autosomal recessive conditions (Table 2). In X-linked recessive conditions, new mutations will contribute a proportion $(1-f)/3$ of all cases, where f is the relative reproductive fitness of affected males. Making allowance for this, the proportion of new cases avoided by retrospective prevention becomes $0{\cdot}05(2+f)$. For dominant conditions with incomplete penetrance, retrospective prevention would only apply to parents who carry the abnormal allele but appear normal. These will produce, again allowing for mutation, a proportion $(1-R)$ of affected children, where R is the degree of penetrance. The risk to further children is $\frac{1}{2}R$ and substituting this for (A) in the above formula gives the proportion of cases preventable from these parents. If $R = \frac{1}{2}$, the result is 0·15 as before, so that the proportion $0{\cdot}15(1-R) = 0{\cdot}075$ of cases may be prevented by retrospective counselling.

In practice several factors may combine to reduce the proportion of cases that may be prevented. After the birth of an affected child in a family, family size may be restricted (Tips and Lynch, 1963) so that fewer children than expected would be at risk. If further children are born *before* the index case is detected, this would also reduce the value of retrospective prevention.

TABLE 2

Proportion of Cases Preventable in the Population

Method of prevention		*Proportion preventable*
Retrospective prevention in affected *sibships*		
Dominant-penetrance	1·0	0
	0·5	0·07
Autosomal recessive		0·15
X-linked recessive		0·05 (2+f)
Complex inheritance		n_1k_1F
Prospective prevention in affected families		
Dominant-penetrance	1·0	f
	0·5	$\frac{1}{2}$f
Autosomal recessive		$\sim$2·5q
X-linked recessive		0·12 +0·73f
Complex inheritance		n_2k_2F
Prospective prevention by parental (carrier) screening		up to 1·0

F—population frequency; f—relative reproduction fitness of affected individuals; n—number of relatives per index case; k—their relative risk; q—gene frequency.

The effectiveness of retrospective prevention decreases as the recurrence risk in sibs falls. In conditions with complex inheritance the average recurrence risk is low and genetic counselling advice is usually not to restrict family size (Roberts, 1962). However, if the index case is severely affected, if the less frequently affected sex is involved or if there is more than one affected person in the family then the recurrence risk in sibs may be high and if so family restriction would then be advised. Summaries of the population frequency (F) and the frequency (kF) in relatives of affected individuals are given by Carter (1965) for various congenital abnormalities and by Newcombe (1966) for several conditions associated with still-birth and infant mortality.

Further cases in affected families account approximately for a proportion (n_1k_1F) of all cases in the population where (n_1) is the average number of *further* births preventable in affected sibships

If family size is normal, (n_1) will be about 0·7 in British families. For several congenital abnormalities and other neonatal conditions, frequencies range from 1 per 2000 to 1 per 200 births, with relative risk (k) values from 10 to 30. The proportion of cases prevented by restricting family size after the birth of an affected child might thus be from 0·005 to a maximum of about 0·05. Thus the yield would be rather low and unlikely to justify the preventive effort involved.

Prospective Prevention

So far prevention has referred only to further cases in affected sibships. What *additional* proportion of cases may be prevented prospectively by detecting parents at risk in the rest of the family? For dominant conditions, the proportion of cases that may be prevented prospectively (allowing for new mutations) is equal to(f)the relative reproductive fitness of affected individuals, or (Rf) where (R) is the level of penetrance (or detection).

In families with a history of an autosomal recessive condition, several relatives will be carrier heterozygotes. The risk to one of marrying an unrelated person who is also a carrier is $2q(1-q)$, where (q) is the frequency of the abnormal allele, and (for the British family size distribution) the risk of their having one or more affected children is about one half. Thus if (q) is low, the total risk to relatives in affected families is also low. It is estimated that, per family (or kindred), there will be on average about seven carrier relatives still at risk. Given $F=q^2$, there will be about $0{\cdot}8q^2$ of sibships with affected children. Combining these figures prospective prevention in the rest of the family would prevent a proportion of about 2q to 3q of all new cases in the population.

For X-linked recessive conditions, female relatives of affected males are possible carriers (heterozygotes) and so their sons may be at high risk. Tests to distinguish carriers from normal women (Emery, 1968) are especially useful in this case. If the discrimination is not complete, it may be possible to combine the test result with information on family history to estimate a woman's likelihood of being a carrier (Murphy, 1968; Emery and Morton, 1968). Of all cases in the population, a proportion $(1-f)/3$ will be due to new mutations in affected males. Of the $2(1-f)/3$ mutations per generation in females it can be estimated that approximately one-third will be lost from the population without their ever giving rise to an affected male. Thus of all cases, a proportion $7(1-f)/9$ will be *first* cases in new families. The remainder $1-(7(1-f)/9)$, is thus the maximum proportion of cases that might be prevented if all further cases in

affected families were prevented. Deducting the proportion (0.5(2+f) which is retrospectively preventable in affected sibships, the proportion preventable prospectively becomes (0·12+0·73f). For severe conditions this proportion is low, but for mild conditions almost all cases will occur in families with some previous disease history and so are prospectively preventable.

For conditions with complex inheritance the proportion of cases that may be prevented prospectively will be about n_2k_2F, as before, where (n_2) refers to the average number of births preventable in the rest of the family and (k_2) is the relative risk of their being affected.

Screening Parents

Another possible approach in the prevention of genetic disease is to screen potential parents. In this way matings at risk might be detected and avoided, family limitation advised or selective abortion (*see* Chapter 9) might be possible. By this means, apart from new mutations, a disease might be *temporarily* eradicated. This procedure is thus the most effective possible in the prevention of genetic disease. However, depending on the form of control used, there may be attendant undesirable changes on the population gene pool (Barker, 1966; Fraser and Motulsky, 1969).

Screening of parents is usually recommended when the disease is frequent, as in sickle cell anaemia in parts of Africa (Allison, 1955) and in haemolytic disease of the newborn. However, the procedure might well be applied to many other less frequent conditions, if it proved economical. Reliable tests for detecting carriers are now available for several genetic diseases (Hsia, 1966). Other possibilities may exist in screening parents at special risk. For example, older mothers are at a higher risk of having children with Down's syndrome (Penrose and Smith, 1966), and in this group there may be justification for routine karotyping of amnistic fluid cells to detect the condition *in utero* (Chapter 12).

Summary of Preventive Methods

In general, screening methods will be most effective in the control of *specific* genetic diseases, but to screen for all conditions would neither be possible nor economically feasible. So screening is likely to be restricted to those diseases for which the returns from prevention best merit the available expenditure.

The proportions of cases preventable by counselling in different kinds of genetic disease are summarized in Table 2. To illustrate the relative value for different modes of inheritance, some exam-

are given in Table 3: for autosomal dominant conditions with complete penetrance (e.g. achondroplasia) and with incomplete penetrance (e.g. R=0·5 in one type of split-hand deformity), for an autosomal recessive condition of high frequency (e.g. cystic fibrosis F=1/2500), for a severe X-linked recessive condition (e.g. Duchenne muscular dystrophy, f = 0) and a less severe X-linked recessive condition (e.g. haemophilia, f = 0·4), and for a common congenital abnormality (e.g. spina bifida and anencephaly, F = 1/200, low relative risk (k) in second and third degree relatives). Retrospective prevention of further cases in affected sibships is useful for autosomal and X-linked recessive diseases. Prospective prevention in the rest of the family is useful for autosomal dominant and X-linked recessive diseases, but is of little value for autosomal recessives. For diseases with complex inheritance and low recurrence risks, only a small proportion of all cases could be prevented by limiting family size either in affected sibships or in the rest of the family.

TABLE 3

Proportion of Cases Preventable by Genetic Counselling
(for details see text)

	Retrospective counselling in sibships	*Prospective counselling in the rest of the family*
Autosomal dominant		
Penetrance 1·0	0	f
0·5	0·07	½f
Autosomal recessive	0·15	0·05
X-linked recessive		
f = 0	0·10	0·12
f = 0·4	0·12	0·41
Complex inheritance (congenital)	0·04	—

DETECTION AND TREATMENT OF ABNORMAL GENOTYPES

Detection of individuals with an abnormal genotype, before they develop symptoms and signs of the disease (i.e. preclinical cases) is of value in two ways. One is to allow an early detection of affected families so that the birth of further cases in the family may thereby

be prevented. This is important in diseases not manifest at birth for it would improve the efficacy of prevention by the methods discussed in the previous sections. The other value in detection of preclinical cases will be to the affected individual himself if early treatment can prevent the development of the disease or improve the prognosis. In this respect the distinction in detection and treatment between genetic and other disease becomes less important as the general principles of preventive and curative medicine apply whatever the aetiology and nature of the disease. The subsequent sections discuss population screening, screening groups at risk and family screening as means of detecting preclinical cases.

Population Screening

Screening the whole population may allow detection of abnormal genotypes and may permit treatment before they manifest the disease. This procedure is now used routinely for several rare but severe genetic diseases, such as phenylketonuria and galactosaemia. The screening tests must be made simple and cheap and should satisfy the criteria (e.g. Nissen-Mayer, 1964) of sensitivity (detecting all true positives) and of specificity (rejecting true negatives). The extent of population screening adopted in preventive medicine will be determined by the costs of screening and of subsequent treatment of affected cases, relative to the benefits accruing to society from control of the disease. However, criteria (economic or social) for assessing the latter are often difficult to establish (Pole, 1968). In view of the very large number of genetic (and non-genetic) diseases amenable to population screening, some selective criteria for screening preference will be needed. Legislation has been introduced in some countries to make mandatory the screening of the newborn (e.g. for phenylketonuria in the USA), thus establishing a Public Health responsibility which could be extended to other diseases if it were justified.

That many possible unforeseen difficulties may arise in practice with population screening is well demonstrated by the results of screening for phenylketonuria. The disease now appears to be much more heterogeneous than was first suspected (Bessman, 1966). Costs of special diets are high and their effectiveness may be queried (Wilson, 1968). Ethnic or regional differences in frequency may lead to testing effort being wasted. Finally, a high risk of mental retardation to normal children of mothers with phenylketonuria has been demonstrated (Frankenburg *et al.*, 1968).

Screening Groups at Risk

The return from a given screening effort may be increased by restricting the tests to groups known to be at an increased risk. If a small proportion (P) at a high relative risk (k_P) is screened, the return per individual screened will be high, but the proportion ($k_P P$) of all cases in the population so detected may be low. In practice a balance must be struck between P and (k_P), but the criteria for doing so are often undefined. The concept of a risk register for handicapping conditions in children (Sheridan, 1962) has been adopted by many Public Health agencies and found to be useful (Oppé, 1967). On the other hand, the use of risk registers has been criticized (Richards and Roberts, 1967) because of their arbitrary nature and large size if an 'acceptable' percentage (80 per cent) of cases are to be detected. Rogers (1968) suggests a two-tier procedure, using simple screening tests for the whole population, followed by special and repeated testing on a high risk group comprising 5–10 per cent of the population.

Family Screening

Relatives of affected individuals form a special group at risk for screening purposes. The yield from family screening will be (k) times that from population screening and a proportion (nkF) of new cases will be detected, where (n) is the number of relatives per index case and (k) is their relative risk. For example, the frequency of simple glaucoma in people over 40 years of age is about 8 per 1000 (Hunt, 1965). With on average 2 sibs per index case and a relative risk (k) of 10 (Paterson, 1965), by screening sibs (who will comprise 1·6 per cent of people over 40) a proportion 0·16 of all new cases might be detected. Other relatives might also be screened, but the return will fall as the relationship with the index case becomes less. In practice to assess the return from family screening, good empirical estimates of relative risks and other statistics will be needed. The numbers and ages of *living* relatives of different degrees of relationship must be determined and the proportion of those that can be contacted and tested must be assessed. Despite these provisos, several of the complex genetic diseases listed in Table 1 might be quite amenable to family screening, if preclinical tests were available and if early treatment was effective.

A GENETIC REGISTER

Within the framework of *Figure 1*, there is a need to store, integrate and process information from different parts of the system. This, in

the widest context, has been termed a genetic register. It would act as a clearing house for information to which case and family details could be referred and from which information about genetic diseases and about families at risk could be obtained.

Recording Role

There are several functions that a genetic register could perform. At the simplest level it might merely form a record of cases attending a genetic counselling clinic. With summarization and follow-up of cases, the work of the clinic and the effectiveness of treatment and advice could be evaluated (Carter, 1967). On a larger scale, all reported cases of certain genetic conditions in an area might be recorded, drawing on records from all medical sources. Changes in frequency of genetic and quasi-genetic conditions could then be monitored (Kallen and Winberg, 1968) and, in the long term, genetic trends in the population might be assessed.

Preventive Role

Changing the focus of the register from a passive recording role to a preventive role would greatly increase its scope and function. Currently there is no regular procedure or defined responsibility for preventing genetic disease, except at the individual level, but a genetic register could provide a basis for this.

On notification of an affected individual, the register and those concerned with genetic disease would become directly involved. Treatment and progress of the affected individual could be supervised and contact maintained in case new treatments became available. Relatives at high risk, or perhaps all close relatives, might be registered along with their period of risk and then, if agreeable, they could be counselled appropriately. On the other hand, reassuring relatives at low risk forms a large part of genetic counselling work (Carter, 1967) and is important to the family, as judged by the previous and subsequent family reproductive history (Tips and Lynch, 1963).

Register Design and Operation

Acheson (1967) has shown the feasibility of storing and linking personal records from different sources and has discussed the advantages of record linkage systems in organization and in research. However, a general medical record linkage system may be too large and too general to serve the special needs of medical genetics, or

other specialized branches of medicine. Rather, different groups are likely to be motivated to develop registers for special purposes and for their own use. For example, special registers are being used for psychiatric (Baldwin *et al.*, 1965) and iatrogenic disease (Crookes, 1968). It is important that registers for different geographical areas and for different diseases should be made compatible (in personal identification) with each other and with the general record linkage system being used. This would allow a wide scope in the study of diseases, their causes and associations, and would be most useful in locating and maintaining contact with individuals affected or at risk.

In designing a genetic register, it is important to define the objectives and scope of the system. Initially these may be restricted but they would be widened later as experience grew and if the value of the register were proven. There are several distinct stages in an operational system for the prevention and treatment of genetic disease. These are: (1) detection; (2) notification; (3) treatment; (4) counselling; (5) detection of relatives at risk; (6) continued supervision of individuals concerned; and (7) feedback of information to the system.

Detection rates may be improved by further medical education on genetic disease and by feedback of information from the genetic register to the medical profession. Alternatively, special screening tests at periods of risk may be initiated. The next stage, notification of cases to the register, is crucial but will require much effort and organization. A routine notification on diagnosis could be requested (with bonus payment) or made mandatory by legislation if the percentage of cases reported by voluntary means was too low. Alternatively, search through medical record linkage might be feasible in the future.

The next critical stage is in the detection of relatives at high genetic risk. This is a major function of a genetic register and would be an innovation in medical practice. Relatives of index cases would be reviewed and a routine procedure for locating, testing and counselling those relatives deemed to be at high risk would be instituted. In addition, affected individuals or those persons still at risk could be continually supervised. A major problem in long-term recording will be to keep the genetic register up-to-date with changes in family state and with migration from the area (Acheson, 1967; Acheson and Forbes, 1968). Linkage with vital records or with Health Service records may be possible. However, an annual review for each family of its health status, family changes and changes in address may be more effective in keeping the register information relevant and would make follow-up studies routine.

Research Role

The main value of a genetic register in research would be to provide a ready source of material for the study of genetic disease and of its relation to other agencies. Of special merit in this regard would be the inclusion of a random sample of unaffected control families. These would provide statistics about the normal population for comparison with families ascertained because of genetic disease. Another research role would be the appraisal of the register system and of current detection and preventive methods. Then, by feedback, their effectiveness in the prevention of genetic disease might be improved.

EFFECTS ON THE GENE POOL

Prevention of genetic disease may lead to changes in the population gene pool. These may be quite difficult to measure in practice for the trends will be small, the time lag long and there will be observational and environmental differences to take into account. Possible changes may be estimated algebraically, given a set of assumptions about frequency, mode of inheritance and about the relative reproductive fitness of different genotypes. However, the relative fitness is rarely known accurately and it may vary with time and environment or be modified by eugenic measures. The algebraic solutions will thus be generally inadequate for making long-term predictions but they may be sufficient to provide a useful guide to the direction and extent of short-term changes.

Simply Inherited Conditions

Retrospective prevention of the birth of further children to affected sibships may cause some reduction in the frequency of abnormal alleles but the reduction will be small because only affected sibships are involved. Prospective prevention, dealing with the rest of the affected family may allow rather larger reductions in frequency of abnormal alleles, especially for dominant and X-linked conditions for which prospective prevention is more effective (Table 2).

For rare severe conditions, maintained at equilibrium by mutation, survival and reproduction of affected individuals will lead to increases in frequency of the condition in the next generation. The increases will be *proportional* to $(1-f)$, $(1-f)/2$ and $2q(1-f)$ for dominant, X-linked and autosomal recessive conditions respectively where (f) is the original relative fitness of affected individuals and

(q) is the equilibrium gene frequency. If (f) is low initially, the proportional increases in frequency of the condition can be quite large for dominant and X-linked conditions, but will be small for autosomal diseases (from 0·2 to 4·0 per cent per generation).

If a condition is maintained by heterozygote advantage, survival of recessive homozygotes may lead to much larger increases in frequency in subsequent generations. The *proportional* increase in *gene* frequency for an abnormal recessive allele is approximately $(1-f)/f$, assuming that the initial gene frequency is low and that (f) the fitness of the two homozygote genotypes approaches that of the heterozygote genotype. The same result holds if double heterozygote matings are prevented. For example, with cystic fibrosis ($q=0{\cdot}02$, $f=0{\cdot}9$; Knudson, Wayne and Hallett, 1967) the *proportional* changes in gene frequency and in frequency of the condition (on random mating) would be about 10 per cent and 22 per cent per generation respectively.

Conditions with Complex Inheritance

Many of the diseases with complex inheritance (Table 1) have their onset largely toward the end of reproductive life, so they will have little effect on the gene pool. However, for the congenital abnormalities, survival and reproduction of affected individuals may lead to changes in subsequent generations. If the original frequency is (F), the proportion of matings with one affected parent would then be (2F). Children from these matings will have a higher frequency (kF) of the condition so the average frequency in the next generation should rise to $F(1+2kF)$. For example, using data from Carter (1961), it can be estimated that if all cases of pyloric stenosis were to survive and have children, the population frequency would rise from 0·5 to 0·54 per cent in males and from 0·1 to 0·116 per cent in females in one generation.

Some of the methods currently used to prevent and treat genetic disease may thus result in somewhat higher frequencies in future generations. However, it may be quite possible to reduce or reverse any unfavourable trends by modifying the preventive methods being used or by counselling the individuals concerned on their social (and genetic) responsibilities.

Eugenic Measures

Plans to reduce the frequency of abnormal genes in the population rather than merely prevent immediate genetic disease, are beginning to be discussed (Fraser and Motulsky, 1969). For example, selective

abortion of female foetuses if the father has an X-linked defect would quickly reduce the population frequency from $3u/(1-f)$ to ($3u$ where (u) is the mutation rate and (f) is the relative reproductive fitness of affected males. It may be possible to eliminate abnormal alleles causing certain disease from the population, or to reduce their frequency to a low level, maintained by mutation. Fraser and Motulsky (1969) have shown that for an autosomal recessive condition the proportion of selective abortions required to eliminate the abnormal allele is $4q(1+2q) / (1+3q)^2$. For cystic fibrosis in Caucasians ($q=0{\cdot}02$) this would represent about 7 per cent of all pregnancies in one generation.

CONCLUSIONS

There are many people in the population who are at risk from genetic disease but special measures are required for their ascertainment. Relatives of affected cases form a special class for they can be readily identified and may be at high risk. For them, the problem of preventing further disease is largely an operational problem of detection and notification of affected cases, followed by the location, testing and counselling of relatives at risk. Such a procedure would seem to be quite feasible in practice and should yield a good return on detection and testing effort.

However, of all genetic disease in the population, only a proportion can be avoided by preventing further cases in 'affected families'. An alternative is to try to detect individuals, or families, at risk in the general population. The difficulty here lies in the large number of possible genetic conditions (McKusick, 1966) and their individual rarity. Screening tests are now available for many genetic diseases. However, there is a limit to the number of conditions that can be screened for and some selective criteria, such as prevalence, severity or value of treatment, may be needed to establish priority in usage. Current screening tests are mostly aimed at detecting and treating affected individuals. A far more effective procedure, in control and prevention of many simply inherited diseases, would be to screen parents and detect those matings at risk so as to prevent the birth of affected children. This would be the method of choice in prevention of genetic disease if screening tests were available and if the return from prevention justified the expenditure involved.

In prevention of genetic disease much depends on public understanding and co-operation. Social and ethical values are changing gradually, and family planning, voluntary sterilization, legalized abortion and other practices affecting reproduction are being increasing

used. These changes in attitude and custom may be helpful in the prevention of genetic disease and they need to be considered and exploited. For example, selective abortion provides a very useful tool in the prevention or control of certain diseases (*see* Chapter 9). However, a far simpler and more general tool, euthanasia of defective newborn, is not yet ethically acceptable though it may be more humane than 'salvage' (Forrester, 1965) in severe incurable diseases. In general, as society becomes better informed and develops a more rational and responsible attitude to reproduction, greater scope will develop for the prevention of genetic disease.

Finally, in practice, the costs of detection, treatment and prevention of genetic disease must be related to the returns achieved. An interesting evaluation of this kind has been done for several prescriptive screening practices (McKeown, 1968) including four genetic diseases. However, the cost–benefit criteria of economics (Weisbrod, 1961) may not be wholly suitable in medicine and genetics. On the other hand, there does not seem to be any equivalent basis for evaluating the social benefits of disease prevention (Pole, 1968).

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ADDENDUM

McKusick (1969, *J. chron. Dis.*, **22**, 1–7) has recently discussed family follow-up in the early detection and treatment of genetic disease and has outlined a Family Oriented, Medical Records System (FOMERS). In our system the ascertainment and preventive aspects of the problem are also emphasized and for this reason, and in order to differentiate between the two systems, we would like to refer to our system as a Register for the Ascertainment and Prevention of Inherited Disease (RAPID).

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A statistical and genetical study of diabetes

I. Prevalence and morbidity

By D. S. FALCONER,* L. J. P. DUNCAN† and CHARLES SMITH‡

INTRODUCTION

The main reason for the collection of the data described here was to obtain estimates of the age-specific prevalence of diabetes mellitus in Edinburgh, Scotland, for use in a genetic study, the results of which are described in the second paper of this series (Smith, Duncan & Falconer, in preparation). The variable age of onset and the increasing prevalence with age, have been adequately documented by several authors in various countries (e.g. Simpson, 1964; College of General Practitioners, 1962; reviews by Pyke, 1968; Malins, 1968). Consideration of the prevalence figures in conjunction with the age of onset, however, makes some analyses possible which we think have not been attempted before, and these are the subject of the present paper.

The prevalence in any particular age group of the population is made up of diabetics whose onset occurred at different ages and who have had the disease for different periods of time. Subdivision of the prevalence figures on the basis of onset age shows that the diabetics in any cohort contain fewer who were diagnosed at earlier dates than would be expected from the current incidences of new cases: in other words the frequency of diabetics in the current population is progressively reduced with earlier date of diagnosis and with increasing duration of the disease. This reduction of frequency may reflect either a lower detection rate in the past than at present or a higher rate of mortality among diabetics than among non-diabetics, or it may be due partly to both causes. It has not been possible with the current data to discriminate between these causes, but the analyses lead to estimates of the limits of their effects if either were the sole cause of the reduction of frequency observed.

A related problem is the estimation of the age-specific morbidity risks. The distribution of onset age among the current population of diabetics will not give a valid estimate if the detection rate has changed or if there is differential mortality. Unbiased estimates of the morbidity risks at the present time can, however, be obtained by making proper allowance for the duration of the disease.

Two other interesting questions arise from the age-specific morbidity risks. The relation of the morbidity risk to age may give evidence on the question whether juvenile and adult diabetes are distinct entities. And, cumulation of the morbidity risks leads to an estimate of the 'potential' prevalence, which shows the prevalence that must be expected in the future if the detection rate continues at its present level and if any differential mortality of diabetics that there may be is eliminated by improved treatment.

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SOURCES OF DATA

Ascertainment

The intention was to estimate the age-specific prevalence and the distribution of onset a by ascertainment that was as nearly complete as possible. The criteria used in the ascertainme of diabetics were simply: (1) that they had been diagnosed as diabetic by a member of t medical profession, and (2) that they were confirmed to be alive and living in the city Edinburgh at 1 January 1968. Name, sex, address, current age, age at onset and current trea ment (diet alone, oral hypoglycaemic, or insulin) were recorded for each individual.

The search for persons with diabetes proceeded in several stages and is summarized in Table First a list of 2512 persons attending the Royal Infirmary Diabetic Department was prepare from current files. To this was added another 368 names from files of patients whose visits the clinic had lapsed for 2 to 3 years. All other Edinburgh hospitals, medical and para-medi institutions were contacted and these supplied names of 437 more persons with diabetes.

Table 1. *Estimation of the number of persons with diabetes, alive and in Edinburgh at 1 January 1968*

Source	Number
Current diabetes clinic files	2512
Lapsed diabetes clinic files	368
Other hospitals	437
Additions by general practitioners	150
Additions from questionnaire checks	24
Sundry other additions	20
	3511
Rejections by general practitioners as:	
(1) Dead	380
(2) Left Edinburgh	71
(3) Not diabetic	5
(4) Not known	14
Other sundry rejections	76
	546
Total persons with diabetes confirmed	2965
Number with incomplete records	33
Number used for analyses	2932

From the 3317 names tabulated, lists were prepared for each general practitioner (G.P.) w had on his N.H.S. list patients residing in the city, using information from the hospital files a from the National Health Executive Council (N.H.E.C.) Register to match the patient with G.P. The 263 G.P.s were asked to confirm or reject each patient on their list and to add t names of any others with diabetes in their practice. Almost all the G.P.s (259 = 98 %) retur their amended lists. Of 260 names added to these lists, 110 were already known, but 150 na were genuine additions to the overall list. On the other hand, 380 people were classified by G.P.s as dead, 71 as having left Edinburgh, 14 were not known and 5 did not have diabe A further 76 persons rejected by the G.P.s for unspecified reasons could not be located on N.H.E.C. register for Edinburgh and were excluded from the overall list.

Deletions from the lists would be easier to make than additions, as it would be more diffi for a G.P. to recall names of diabetics not on his list than to review the health status of identi

patients. Many people with mild diabetes, on diet treatment, might not attend the clinic and would not be on the overall list. It was thought that G.P.s might add many such patients, and many old patients to their lists. To some extent this was true (Table 2), there being a somewhat higher proportion of old diabetics among the additions than in the population. However, while there was a lower proportion of insulin-treated cases among additions than in the population, there was a much higher proportion of patients taking an oral hypoglycaemic than was expected.

Table 2. *Comparison of age and treatment among additions and overall*

	Percentage	
	Overall	Additions
Current age		
< 25	4	3
25–44	11	6
45–64	41	37
65+	43	54
Treatment		
Diet	32	29
Oral	36	48
Insulin	32	23

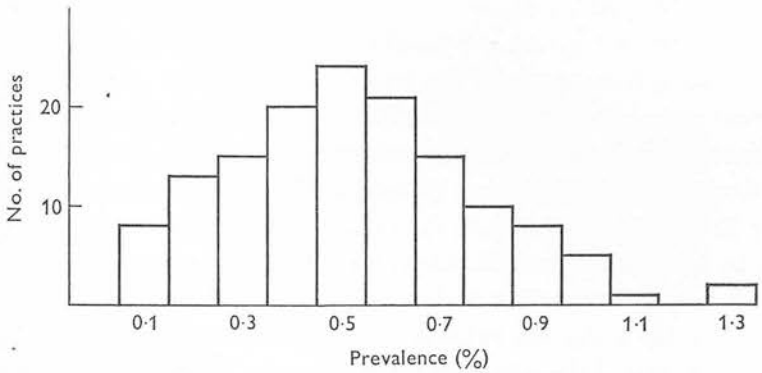

Fig. 1. Distribution of prevalence among general practices.

The prevalence of diabetes in each general practice could be found from the amended G.P. list and the total number of patients in each practice. There was a wide range in prevalence among practices but the distribution was Normal in form (Fig. 1). Several practices were studied in detail, three with low prevalence (A, B and C in Table 3), two with average prevalence (D and E) and two with high prevalence (F and G). The differing age distribution in these practices accounted for some of the differences in prevalence. However, other factors such as income group, social class and doctor's record system and interest may also be involved. In practice E, the practitioner provided a very detailed and complete summary of people with diabetes in his practice. Three new persons with diabetes were found in the seven practices. However, the G.P. files were not always suited to searches for diabetic patients, so the search could not be very thorough.

Two further checks were made, using information from the questionnaire described in the second paper of this series for which diabetics were interviewed about the diabetic status of

their relatives. Seven of those interviewed had been omitted from the overall list. Of 15 relatives said to be diabetic and with complete Edinburgh addresses, 17 were not on the overall list. Of these, 6 were dead or had left Edinburgh, 5 were not known at the address given and could not be traced, 5 confirmed their diabetic status and one was not diabetic.

Table 3. *Prevalence and age distribution of diabetics in seven selected general practices*

Practice	Prevalence (%)	New cases	Age distribution (%) <25	25–44	45–64	>64
Low prevalence						
A	0·19	0	51	25	20	4
B	0·25	2	31	25	29	15
C	0·33	0	37	24	26	13
Average prevalence						
D	0·59	0	46	29	19	7
E	0·59	0	35	25	27	13
High prevalence						
F	0·86	0	20	19	39	22
G	1·39	1	19	21	36	24
Edinburgh	0·63		38	24	25	13

These various searches yielded names of 2965 people confirmed to be diabetic and alive in Edinburgh at 1 January 1968, giving an overall prevalence rate (population 468,000) of 0·63%. This is likely to be an underestimate of the true prevalence since the searches are incomplete and only confirmed cases have been included. Rather than initiate further searches, the extent of the underestimation has been assessed. Omissions from the clinic and hospital lists might add a further 5 to 10 cases. In seven practices studied in detail three new cases were found, so that perhaps another 50 to 100 cases might be found if all practices were so studied. Finally of 15 relatives said to be diabetic and with Edinburgh addresses, 5 confirmed new cases were found. At the same error rate, for some 3000 diabetics in the city, another 50 to 100 cases might be expected. Thus, from these various indications, it is estimated that there may be a further 150 to 300 cases of diagnosed diabetes in Edinburgh, some 5 to 10% of the total, that do not appear on the overall list. Thus the best estimate of the overall prevalence is between 0·66 and 0·69%. The prevalence in the Birmingham study (College of General Practitioners, 1962) was 0·64%.

In the 2 years after the collection of the data had been completed, 63 cases that had been missed came to light from information obtained from death certificates and other sources. Addition of these cases brings the observed prevalence up to 0·65%. These retrospective additions were, however, not included in the computations, partly because the computations had already been completed and the addition of these 63 cases made a hardly appreciable difference but mainly because they were a biased sample, their ages being nearly all over sixty. Thirty-three of the 2965 confirmed cases could not be used for computation because of incomplete records. The total number of diabetics used for computation was therefore 2932.

Population numbers

The distribution of the population of Edinburgh by 10-year age intervals and sex was supplied by the Office of Registrar General for Scotland, being estimates for the June 1967 population

based on the 1961 census and the 1966 partial census reports. The distributions of the two sexes are given in Table 4 for 10-year intervals. To get the distribution by 5-year intervals for 1967, shown in Fig. 2, each 10-year interval was split in the same proportions as those in the full 1961 census.

Table 4. *Numbers of diabetics grouped by current age (at 1 January 1968) and onset age*

	Onset age	Current age 0–9	10–19	20–29	30–39	40–49	50–59	60–69	70–79	80–89	90+	Total	%
Males													
	0–9	4	16	5	5	—	—	—	—	—	—	30	2·4
	10–19	—	17	33	18	10	3	1	—	—	—	82	6·5
	20–29	—	—	21	35	32	7	5	1	—	—	101	8·1
	30–39	—	—	—	23	59	23	15	2	—	—	122	9·7
	40–49	—	—	—	—	68	91	32	2	2	—	195	15·5
	50–59	—	—	—	—	—	159	137	28	3	—	327	26·1
	60–69	—	—	—	—	—	—	183	91	6	—	280	22·3
	70–79	—	—	—	—	—	—	—	83	21	—	104	8·3
	80–89	—	—	—	—	—	—	—	—	13	1	14	1·1
Total diabetics		4	33	59	81	169	283	373	207	45	1	1255	
Population, thousands		39·05	35·93	28·27	26·44	26·37	28·43	21·33	9·91	2·95	0·15	218·7	
Prevalence per thousand*		0·10	0·92	2·09	3·06	6·41	9·95	17·5	20·9	15·3	6·8	5·74	
Females													
	0–9	6	13	10	2	1	—	—	—	—	—	32	1·9
	10–19	—	20	24	11	7	5	—	—	—	—	67	4·0
	20–29	—	—	24	26	22	9	2	—	—	—	83	4·9
	30–39	—	—	—	33	54	34	11	4	1	—	137	8·2
	40–49	—	—	—	—	45	83	63	14	—	—	205	12·2
	50–59	—	—	—	—	—	149	223	79	2	—	453	27·0
	60–69	—	—	—	—	—	—	257	179	21	—	457	27·2
	70–79	—	—	—	—	—	—	—	165	51	—	216	12·9
	80–89	—	—	—	—	—	—	—	—	25	1	26	1·6
	90+	—	—	—	—	—	—	—	—	—	1	1	0·1
Total diabetics		6	33	58	72	129	280	556	441	100	2	1677	
Population, thousands		37·30	35·20	29·70	27·75	29·76	34·27	29·44	19·15	6·55	0·45	249·6	
Prevalence per thousand*		0·16	0·94	1·95	2·59	4·34	8·17	18·8	23·0	15·3	4·4	6·72	

* Allowance for the estimated numbers not ascertained would raise the prevalence figures by between 5 and 10%.

ANALYSIS OF DATA

Methods

The primary data consist of the current age, C (at 1 January 1968) and the onset age, O, of each individual. From these ages, two additional statistics of interest can immediately be obtained: the duration of the disease, D (given by $C-O$) and the year (i.e. date) of diagnosis, Y (given by $1968-D$). These derived statistics, however, are completely correlated, since $Y+D$ is the same for all individuals ($Y+D=1968$).

For the analysis of the data, the individuals must be grouped, and the grouping can be done by any of the three criteria: current age, onset age, or duration and year of diagnosis. In order to understand the implications of the grouping for the analyses that follow it is necessary to

consider the structure of the primary data in detail. The various groupings used were all made by accumulation from a table of current age and onset age in 1-year intervals (i.e. the primary data). Fig. 3 illustrates the upper left corner of this tabulation. The columns are 1-year intervals

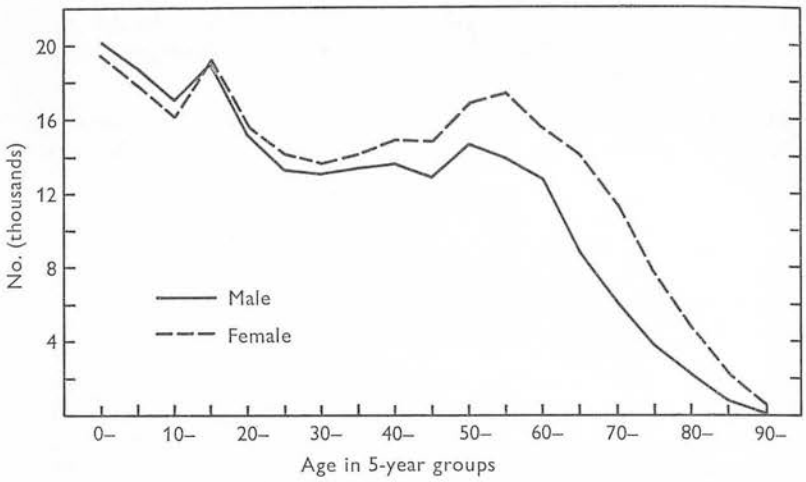

Fig. 2. Age distribution of population in 5-year groups.

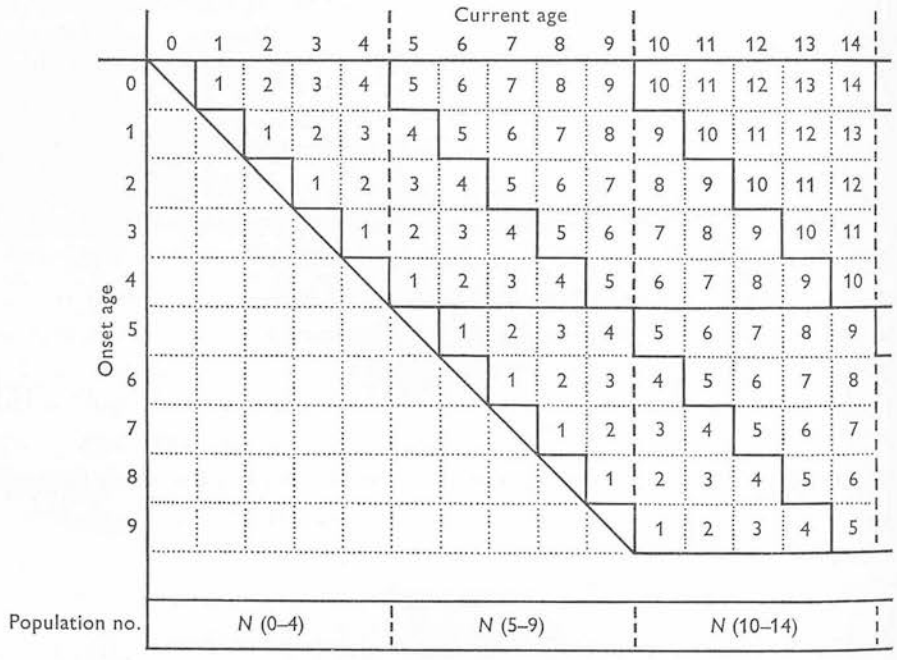

Fig. 3. Structure of the tabulation by single years of current age and onset age, with the duration in years entered in each cell. Further explanation in text.

of current age and the rows are 1-year intervals of onset age. In the actual table used the numbers of diabetics in the data were entered in each cell. In Fig. 3, however, the number shown in each cell is the duration corresponding to each current- and onset-age. Five-year groups of current age are marked by vertical broken lines, and 5-year groups of onset age by horizon-

unbroken lines. Five-year groups of duration are marked by the stepped diagonal lines. At the foot of the table are the population numbers corresponding to each current-age group. The features of the table that have implications for the analyses are as follows.

1. Totalling the numbers of diabetics in the current-age groups (columns) and dividing by the corresponding population number gives the age-specific prevalence.

2. Totalling the numbers of diabetics in the onset-age groups (rows) gives the distribution of onset age among living diabetics.

3. Grouping by current age and by onset age leads to the groups having durations that span twice the grouping interval and that overlap between neighbouring groups. For example, the group with current age 5–9 and onset age 0–4 has durations ranging from 1 to 9 years; and the neighbouring group with current age 10–14 and onset age 0–4 has durations ranging from 6 to 14 years. For this reason grouping by current age and onset age is not suitable for any analysis where the duration is of primary interest. For these analyses the grouping must be done by duration. The main grouping to be used in the subsequent analyses is by onset age and duration.

4. Grouping by onset age and duration has two consequences of importance, which can be seen by consideration of Fig. 3.

(i) Within each onset-age group, duration is correlated with current age, so that the groups with longer durations also have higher current ages.

(ii) The calculation of the frequencies of diabetics in each group is not straightforward because each 5-year group of onset-age and duration spans 9 years of current age. The population numbers in each current-age group represented have therefore to be weighted appropriately in the calculation of the frequencies. Consider for example the group with onset-age 0–4 and duration 5–9. There are 25 single-year cells in the group, of which 15 fall in the current-age group 5–9, and 10 in the current-age group 10–14. The weighted population number appropriate to this group is therefore $0{\cdot}6N_{(5-9)} + 0{\cdot}4N_{(10-14)}$. Division by this number gives the frequency in a 5-year age group. The weightings appropriate to other groupings were calculated in a similar way.

5. Along the diagonal of Fig. 3 are individuals whose onset age is the same as their current age, and whose duration is therefore less than one year. These will be referred to as the 'zero-duration' groups. The accumulation of the numbers of diabetics in the diagonal cells with onset from 0 to 4, for example, gives the zero-duration group in the 0–4 onset-age group. If the single-year cells of Fig. 3 are imagined as being subdivided into months or days, it will be seen that no individual could appear below the diagonal bisecting each cell, because the onset age cannot be greater than the current age. Consequently the number of diabetics recorded in each zero-duration group will be only half the number that would be found by retrospective recording of individuals at their next birthday. Therefore to obtain the true frequency of diabetics with zero-duration (i.e. duration less than 1 year) the observed numbers must be doubled. This point will be further discussed later. The mean duration of the disease in individuals in the zero-duration groups is theoretically 0·5 years.

Prevalence and age of onset

The individuals comprising the data were first grouped by current age (at 1 January 1968) and by onset age. The grouping was done in 5-year and in 10-year intervals. Table 4 gives the numbers of diabetics in 10-year groups of current age and of onset age. Fig. 4 shows the age-

specific prevalence in each sex in 5-year groups of current age. Up to the age of 40 the prevalen is the same in the two sexes; from 40 to 60 it is higher in males, and from 60 to 80 it is a litt higher in females. On the logarithmic scale the increase in prevalence is not far from bein linear; between the ages of 10 and 60 the prevalence increases about $2\frac{1}{2}$-fold in each 10 year or is doubled in each 8 years. The maximum prevalence occurs between 75 and 80 when it 2·3 % in males and 2·6 % in females. If allowance is made for the estimated deficiency i ascertainment the prevalence figures would be increased by between 5 and 10 %, bringing th maximum prevalence to 2·4–2·5 % in males and 2·7–2·9 % in females. Over the age of 80 th

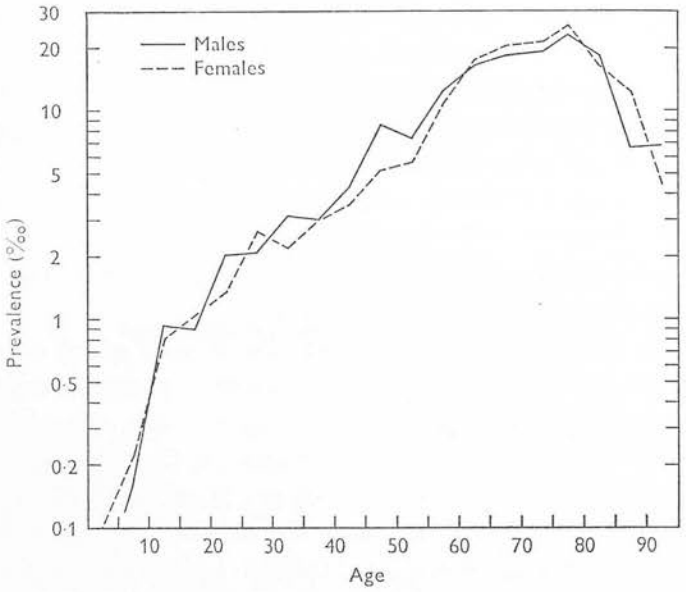

Fig. 4. Observed prevalence, per thousand, in 5-year age groups.

prevalence falls off steeply. This may be due to differential mortality, or it may reflect a di proportionate number of omissions from the records. Diabetics of this age are more likely tha younger ones to be treated by their G.P. rather than in hospital, and so are more likely to hav been missed in the recording.

Fig. 5 shows the distribution of the age of onset in 5-year intervals among the diabetics the data. Earlier onset is more frequent among males than among females and later onset mo frequent among females than among males. The mean age of onset is thus lower in males (45 years) than in females (53·8 years). The most frequent (modal) age of onset is, however, t same in both sexes, i.e. between 60 and 65.

'*Frequency reduction*'

The distribution of diabetics grouped by current age and by onset age, as in Table 4, pos some interesting problems connected with the interpretation of the age-specific prevalence rat and of the distribution of onset age, particularly when these are used to derive the morbidi risks. It is apparent that the numbers in any onset-age group, i.e. the rows of Table 4, are qu different in the different current-age groups (columns). Excepting the cells of the diagonal, t numbers in each onset age decrease rapidly as the current age increases. Allowance for the

distribution of the population by expressing the results as frequencies has little effect on these trends. This reduction of the frequency with increasing current age in any onset-age group will be referred to simply as the 'frequency reduction'. It is clear that the frequency reduction has an important influence on the distribution of age at onset obtained by totalling the rows of Table 4 and on the age-specific prevalence, obtained by totalling the columns. Proper account must therefore be taken of it in calculating the morbidity risks. Before going on to the calculation of the morbidity risks, we shall consider briefly the possible causes of the frequency reduction.

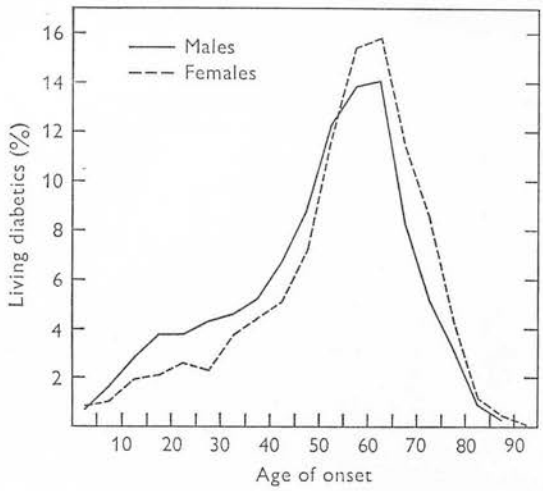

Fig. 5. Distribution of onset age among living diabetics. Onset age in 5-year age groups.

Fig. 3 shows that in any onset-age group, current age is correlated with the duration of the disease and, as explained in the methods section, with the date of diagnosis. Therefore the frequency reduction may be associated either with the duration of the disease or with the date of diagnosis. The possible causes are:

(i) Differential migration: a greater tendency for diabetics to leave the area under study or for non-diabetics to enter it.

(ii) Recording loss: a tendency for diabetics diagnosed at earlier dates to be lost from the records.

(iii) Remission, or cure.

(iv) Differential mortality: a higher rate of mortality of diabetics than of non-diabetics in the same cohort.

(v) Increasing detection rate: due to either (*a*) a higher proportion of the diabetics in the population being detected, or (*b*) a real increase in the incidence of diabetes as a result of some environmental change unconnected with diagnosis.

The first three of these seem unlikely to cause so great an effect and we shall assume that the frequency reduction reflects either differential mortality or increasing detection rate. If mortality is the cause, the frequency reduction will be associated with the duration of the disease, while if increasing detection rate is the cause it will be associated with the date of diagnosis. But it is not possible to discriminate between these two by any direct means because the duration and the date of diagnosis are completely correlated. We shall, however, return to this question later.

Morbidity risks

The age-specific annual incidence, to be called the morbidity risk is the probability that a individual will be diagnosed as diabetic within any particular year of his age. This is the age-specific frequency of new cases. The frequency of living diabetics in each onset-age group will not serve to estimate the age-specific frequency of new cases, because the frequency falls off with increasing duration of the disease. Consequently, if any but the very recently diagnosed cases are to be used to estimate the morbidity risk, the duration has to be taken into account.

Table 5. *Numbers of diabetics grouped by onset age and duration*

Onset age	Mean current age	Duration (years) 0	1–4	5–9	10–14	15–19	20–24	25–29	30–34	35–39	40–44	45–49	Total
Males													
0–9	18	1	5	8	5	4	4	3	—	—	—	—	30
10–19	29	3	18	16	11	12	6	8	4	3	0	1	82
20–29	39	4	20	16	17	17	12	7	3	2	2	1	101
30–39	48	5	19	30	23	14	14	5	10	1	1	—	122
40–49	54	13	58	58	34	17	9	2	2	2	—	—	195
50–59	61	30	139	94	36	21	4	2	1	—	—	—	327
60–69	69	34	133	82	23	7	1	—	—	—	—	—	280
70–79	77	15	56	30	3	—	—	—	—	—	—	—	104
80–89	85	6	7	1	—	—	—	—	—	—	—	—	14
Totals		111	455	335	152	92	50	27	20	8	3	2	1255
Females													
0–9	18	1	6	6	9	5	1	2	1	0	1	—	32
10–19	29	3	16	13	8	7	8	4	3	3	1	1	67
20–29	38	3	18	18	10	15	8	2	5	4	—	—	83
30–39	48	5	34	20	26	20	9	12	5	5	1	—	137
40–49	57	10	42	39	44	35	19	7	6	3	—	—	205
50–59	64	29	130	123	87	61	18	4	1	—	—	—	453
60–69	70	41	195	141	58	20	2	—	—	—	—	—	457
70–79	78	35	107	62	12	—	—	—	—	—	—	—	216
80–89	86	7	16	3	—	—	—	—	—	—	—	—	26
90+	93	—	1	—	—	—	—	—	—	—	—	—	1
Totals		134	565	425	254	163	65	31	21	15	3	1	1677

Table 5 shows the numbers of diabetics grouped by onset age and duration, as explained in the Methods section. Onset ages are grouped in 10-year intervals and durations in 5-year intervals; the groups with durations 0–4 years are divided into two—those with 'zero-duration' and those with 1–4 years' duration. The numbers of diabetics in these groups were converted to frequencies in their own cohorts, in the manner already explained. This gave the frequencies in 5-year age-groups of the population. These frequencies were then divided by 5 to obtain the average annual incidence of new cases as estimated from the diabetics in each cell of the tabulation. The annual incidences in the zero-duration groups were based on twice the observed numbers, for the reasons given above. The annual incidences are given in Table 6.

Each row of Table 6 contains a series of estimates of the morbidity risk at the age to which the row refers, i.e. the onset age. The successive estimates, from left to right along the row, are derived from diabetics who were diagnosed at successively earlier dates, and who have had the disease for successively longer durations. The frequency reduction along the rows is a

apparent. The true morbidity risk to be estimated is the annual incidence at the date of the study – 1968 – which should be based on diabetics whose duration is strictly zero. Direct, but not fully satisfactory, estimates can be obtained from the annual incidences in the groups with the shortest durations, i.e. the groups with 'zero-duration' and 1–4 years duration. The age-specific morbidity risks derived from these groups are shown in Fig. 6. The zero-duration groups give much higher estimates than the groups with 1–4 years' duration, almost twice as great in people over 30.

Table 6. *Annual incidence of new cases per* 100,000, *estimated from the numbers in Table* 5

Median onset age	Median year of diagnosis, and duration (years)										
	1968	1965	1960	1955	1950	1945	1940	1935	1930	1925	1920
	0·5	3	7·5	12·5	17·5	22·5	27·5	32·5	37·5	42·5	47·5
Males											
5	5·1	3·3	4·5	2·8	2·5	2·9	2·3	—	—	—	—
15	17	13	10	8·0	9·1	4·5	6·0	3·0	2·2	—	0·8
25	28	18	12	13	13	9·0	5·0	2·2	1·6	2·1	1·6
35	38	18	22	17	10	10	4·1	11	1·6	2·4	—
45	99	54	42	25	14	9·6	3·1	4·8	8·4	—	—
55	211	127	77	38	33	9·6	8·4	9·4	—	—	—
65	319	184	127	55	29	9·4	—	—	—	—	—
75	303	176	126	28	—	—	—	—	—	—	—
85	407	91	34	—	—	—	—	—	—	—	—
Females											
5	5·4	4·2	3·5	5·1	3·1	0·7	1·4	0·7	—	0·7	—
15	17	11	8·0	5·5	5·0	5·7	2·7	2·0	1·8	0·6	0·6
25	20	16	13	7·1	10	5·2	1·2	3·0	2·5	—	—
35	36	30	14	17	12	5·3	7·6	3·6	4·4	1·2	—
45	67	34	24	26	22	14	6·1	7·3	6·0	—	—
55	169	97	78	63	53	22	8·0	4·1	—	—	—
65	278	178	123	71	40	8·2	—	—	—	—	—
75	366	170	124	49	—	—	—	—	—	—	—
85	214	89	37	—	—	—	—	—	—	—	—

There are two reasons why the zero-duration groups are unsatisfactory for estimating the morbidity risks. First, they represent only a small part of the total data and the numbers in the groups are small. Secondly, the argument leading to the doubling of the observed numbers assumes that the collection of the data was effectively instantaneous. This is unlikely to be true in practice. Though all ages were recorded as at a single date – 1 January 1968 – the data were collected over a period of several months and new cases diagnosed during this period would tend to make the recording partially retrospective and so swell the numbers in the zero-duration groups. It will be shown later that the numbers in the zero-duration groups are higher than is compatible with the rest of the data, and represent about 65 % of the new cases arising in 1-year, instead of 50 % as expected if recording were instantaneous.

The estimates derived from the groups with 1–4 years duration have the advantage that these groups contain the largest numbers of individuals and so the estimates are the least subject to sampling error. But the frequency reduction over the period of 1–4 years may not be negligible and for this reason the estimates are likely to be too low.

Though the two estimates presented so far are not fully satisfactory, they provide a valid comparison between the two sexes. The graphs in Fig. 6 show that the morbidity risks are higher in males than in females and the two estimates are essentially consistent in the differences shown. There is little difference below the age of about 20 and above about 60. The greatest difference is between about 40 and 60, when the risk to males is about 1·5 times the risk to females.

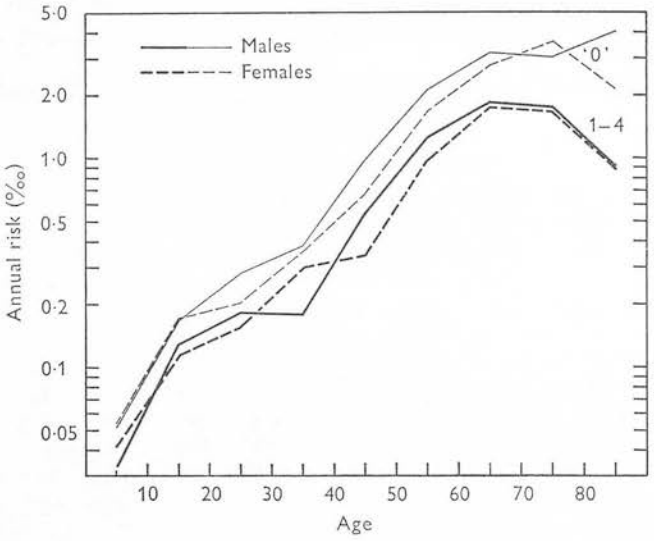

Fig. 6. Morbidity risks per thousand per annum, estimated from the frequencies of diabetics with 'zero-duration' (thin lines) and with durations of 1–4 years (thick lines). Ages in 10-year groups.

The best estimate of the true morbidity risk is to be obtained by utilizing all the data in each row of Table 6, and making proper allowance for the frequency reduction. Figs. 7 and 8 show for males and females respectively, the morbidity risks estimated from the first four columns of Table 6, i.e. the groups with durations of 'zero', 1–4, 5–9 and 10–14 years. It is clear that on the logarithmic scale the estimates fall off fairly regularly with increasing duration. By evaluating the rate at which the estimates fall off we can extrapolate back to a duration of zero and so estimate the true morbidity risk. This was done by fitting linear regressions, as follows.

The logarithm of the estimate of annual morbidity risk was plotted against the mean duration of the group. This was done separately for each group of onset ages, and the results are shown in Fig. 9. The graphs show an essentially linear relationship between the logarithm of the risk and the duration in years in each onset-age group, but the slopes differ between the groups. Extrapolation to a duration of zero was made by calculating the intercept of the linear regression line fitted to the points. The intercepts are marked on the vertical axes of the graphs. The regression coefficients, estimating the slopes, will be used in later sections. It would have been an advantage if the points used to calculate the regressions could have been weighted by their reliability, since some are based on much larger numbers of diabetics than others. But to weight by the number on which each point is based would have introduced a bias, since the numbers observed are subject to sampling error and the estimate itself is dependent on the number observed. So the regressions were calculated without weighting. The points representing the longer durations, however, are based on very small numbers of diabetics, and it seemed desirable

to exclude these. Five diabetics in the group were set arbitrarily as the smallest number for inclusion. The points for 'zero duration' were also excluded because of their uncertain validity, as explained above. The points to which the regression lines were fitted are connected by full lines in the graphs in Fig. 9.

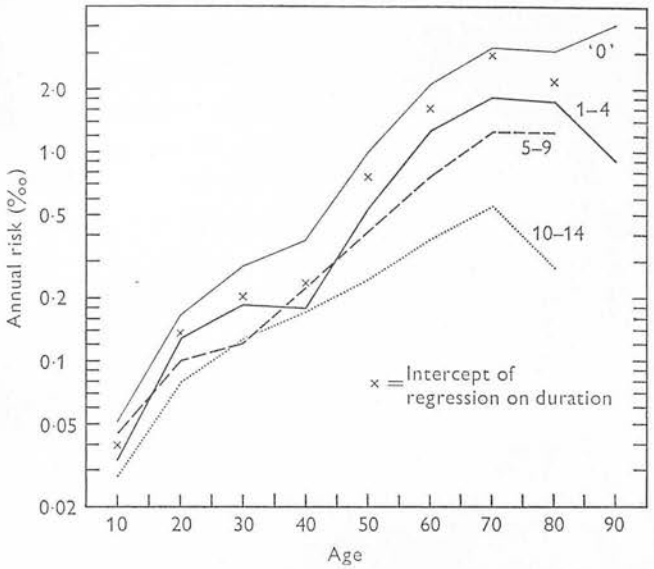

Fig. 7. Morbidity risks of males, per thousand per annum, estimated from the frequencies of diabetics with different durations as shown. The crosses are the estimates from the regression intercepts as explained in the text. Ages in 10-year groups.

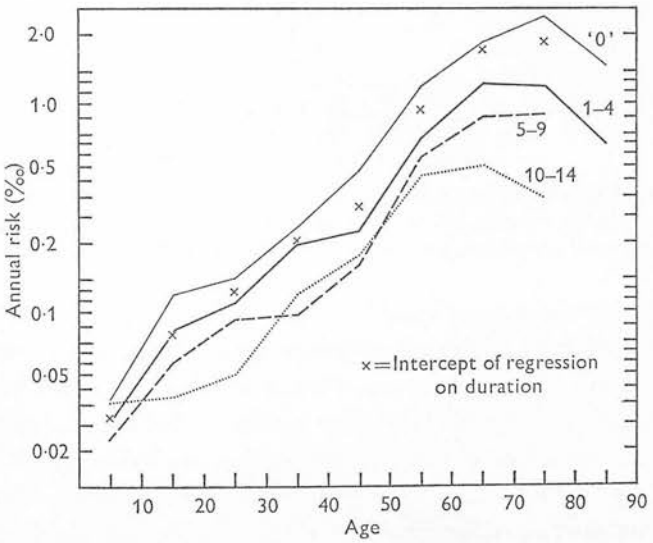

Fig. 8. Morbidity risks of females, as Fig. 7.

The morbidity risks estimated from the regression intercepts, are shown by crosses in Figs. 7 and 8. These estimates all fall fairly regularly between the values obtained from the 'zero-duration' groups and the 1–4 years duration groups. This shows that the morbidity risks were over-estimated by doubling the numbers in the 'zero-duration' groups. Averaging all age groups

and both sexes, the estimates from the 'zero-duration' groups are 1·3 times the estimates from the regression intercepts. The numbers recorded with 'zero-duration' were therefore 1·3 times the expected number of new cases in a half year, or 0·65 times the expected number of new cases in a full year.

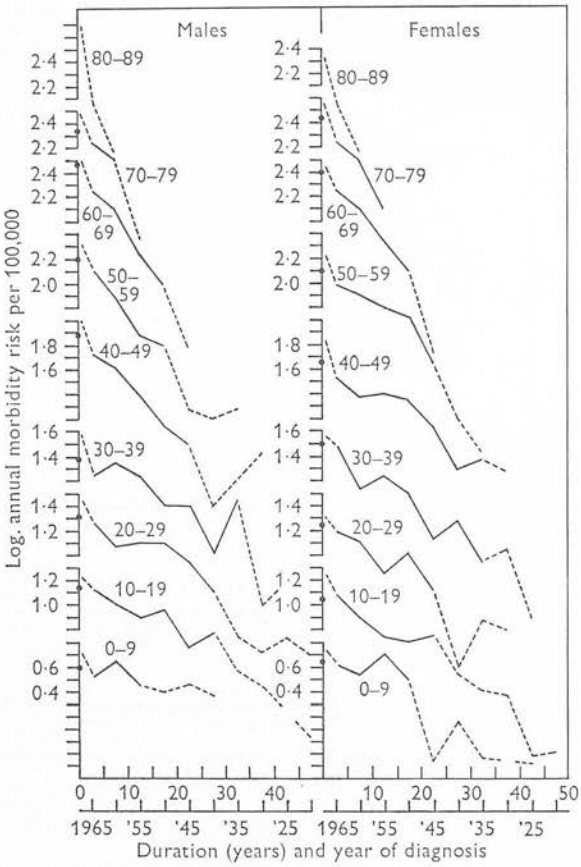

Fig. 9. Log of annual morbidity risk per 100,000 plotted against duration and year of diagnosis. Each graph refers to a 10-year group of onset age, as indicated. Linear regressions fitted to the points connected by solid lines have intercepts on the morbidity axes marked by the dots.

The reliability of the various estimates of the morbidity risks described above may be summarized as follows. The 'zero-duration' groups give estimates that are unreliable because the period at risk is uncertain and because of small numbers. The 1–4 years duration groups give estimates that are biased by the frequency reduction but are the most reliable in respect of numbers. The regression intercepts give estimates that are unbiased but are unreliable in the youngest and oldest age groups where the regressions are based on very few points. The results were combined in a somewhat arbitrary manner, by drawing smoothed curves taking account both of the unbiased intercept estimates and of the trend of the more reliable 1–4 years duration groups. These curves are shown in Fig. 10.

Early onset

One of the chief reasons for calculating the true annual morbidity risks at different ages was to see if there is any indication of a natural gap in the overlap between early- and late-onset

diabetes. If these were clearly distinct diseases with little overlap of onset ages there would be a reduced morbidity risk at ages between the last of the early-onset cases and the first of the late-onset cases. Or, if there were some overlap of onset ages the morbidity curve would have an inflexion or discontinuity in its rate of increase. There is in fact some indication of a discontinuity in males, and possibly also in females, between the ages of about 20 and 40. The observed morbidity curve is therefore compatible with early- and late-onset diabetes being aetiologically distinct; but if they are, there must be a wide overlap between the two in the ages of onset. If the observed morbidity risk is the sum of two separate risks, the onset age of the juvenile form must extend up to about 35 or 40, and the onset age of the adult form must extend down to about 20. The evidence for there being two separate distributions of risk is, however, far from conclusive and the discontinuities in the observed morbidity curves may be no more than sampling error.

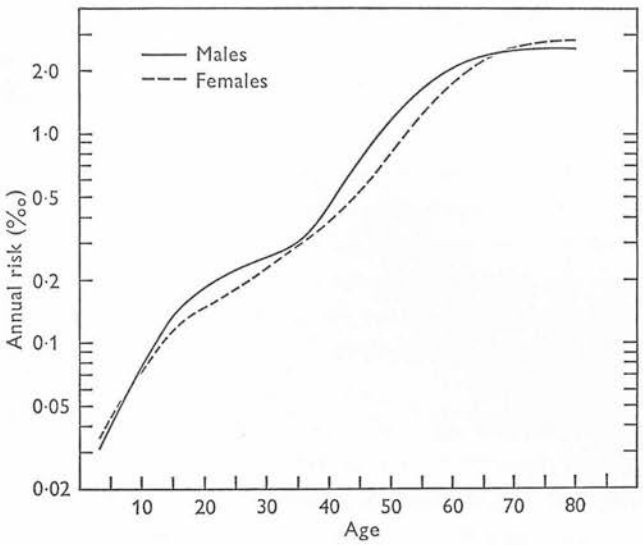

Fig. 10. Age-specific annual morbidity risk, per thousand. Smoothed curves drawn from Figs. 7 and 8.

Potential prevalence

By cumulating the morbidity risks a 'potential prevalence' can be calculated. The cumulated risks, estimated from the regression intercepts, are shown in Fig. 11 with the observed prevalences for comparison. The potential prevalence is the prevalence that would be found if there were no frequency reduction. If the frequency reduction is due to mortality, the potential prevalence shows what the prevalence would be in the absence of differential mortality, and what it may be expected to be in the future if methods of treatment are perfected. If the frequency reduction is due to increasing detection rates, the potential prevalence shows what must be expected in the future if the detection rate continues at its present level. The potential prevalence exceeds 1 % by the age of 50 and rises to about 8 % at 80. It is double the actual prevalence at the age of about 60 and eight times at 80.

Mortality

The two most likely causes of the frequency reduction were stated earlier to be differential mortality and increasing detection rate. The rate at which the frequency of diabetics is reduced with increasing duration, or with earlier date of diagnosis, allows us to set upper limits to either of these causes on the assumption that the one under discussion is the sole cause of the frequency reduction. Mortality is considered in this section and detection rate in the next. In both cases the estimates are derived from the regression coefficients fitted to the graphs in Fig. 9, described in the section on morbidity risks.

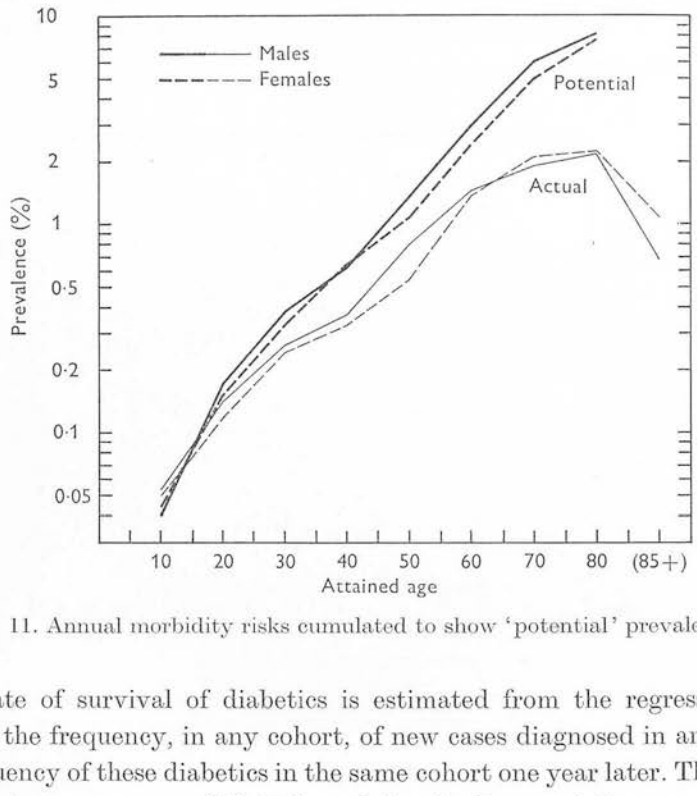

Fig. 11. Annual morbidity risks cumulated to show 'potential' prevalence.

The relative rate of survival of diabetics is estimated from the regression coefficient as follows. Let q_0 be the frequency, in any cohort, of new cases diagnosed in any particular year. Let q_1 be the frequency of these diabetics in the same cohort one year later. Then $q_1/q_0 = k$ gives the rate of survival over one year of diabetics relative to the population as a whole. Now let q_d be the frequency in the same cohort after a duration of d years, and assume that k remains constant over this period. Then $q_d = q_0 k^d$, or $\log q_d = \log q_0 + (\log k)d$. This equation is equivalent to a linear regression equation, $\log k$ being the slope from which the relative survival, k, is estimated. The near-linearity of the graphs shows that k is constant within each age group over the range of duration covered, and the assumption of constancy is therefore justified, even though k differs between age groups.

The relative rate of survival, k, is related to the mortality as follows. Let a = the annual rate of mortality from all causes in non-diabetics. The annual rate of survival is then $1-a$. Let b = the additional probability of death associated with diabetes. Deaths associated with diabetes need not necessarily have diabetes as the primary cause; they can have any cause in which the risk is increased by diabetes. Diabetics are subject to both risks, from all causes associated with diabetes, and the additional risks associated with diabetes. The ann

mortality rate among diabetics is then the joint probability, $a+b-ab$, and the survival rate is $1-(a+b-ab) = (1-a)(1-b)$. The relative rate of survival, estimated from the regression coefficients, becomes in these terms,

$$k = \frac{(1-a)(1-b)}{1-a} = 1-b,$$

whence, $1-k = b$. Thus, $1-k$ estimates the additional annual mortality risk associated with diabetes.

It has already been noted from Fig. 9 that the slopes of the graphs differ according to the onset age of the group, groups with higher onset age having greater slopes and therefore higher additional mortality risks. One would have expected the additional risk to diabetics to be much greater in early onset than in late onset cases, because juvenile diabetes is generally more severe. A difficulty inherent in the data is that onset age is largely confounded with current age and the correlation between them is high. This can be seen from the tabulation by onset age and current age in Table 4, where the correlation between the onset age and the current age of the groups (cells of the table) is 0·83. Thus the greater additional risks in the older groups may be associated with their higher current age rather than their higher onset age. To try to resolve this point, analyses of a similar form to those just described were carried out on the data grouped by current age and duration. The two groupings, however, led to substantially the same estimates of the additional mortality when compared on the same age-criterion, i.e. the mean current age in both groupings or the mean onset age in both groupings. It was therefore not possible to decide whether the increasing risk is associated with onset age or with current age.

The estimates of the additional risk, b, calculated from both onset-age and current-age groups are shown in Fig. 12, with the population mortality, estimating a, for comparison. The population mortality rates are those for all Scotland in 1967, given in Table 60 of the Report of the Registrar General for Scotland, 1967. The estimates from the onset-age groups are plotted against the mean current ages of the groups in order to make all risks comparable on the same age criterion. The additional risk to diabetics (b), as already stated, increases with increasing age. It is about 1–2 % at age 20 and rises to about 10 % at age 80. The population mortality, estimating the risk (a) from all other causes, starts at a much lower level, but rises at a much faster rate, so that at age 20 the additional risk to diabetics is about twenty times the population mortality, but at age 80 the two are about equal. The relative mortality of diabetics, expressed as the total mortality of diabetics relative to the population mortality $(a+b-ab)/a$, is about 20 at age 20 and about 2 at age 80. Thus, relative to the population mortality, the mortality of young diabetics is higher than that of old diabetics, and this correlates with the relation between severity and age.

These estimates are upper limits of the mortality rates; how do they compare with direct estimates of relative mortality? For comparison we have calculated the additional risk to diabetics (b) from two other sources of data. Post (1962) gives the proportions of diabetics and of the population in quinquennial groups who survive into the next quinquennium. In our notations these statistics are $[(1-a)(1-b)]^5$ and $(1-a)^5$ respectively, from which we have calculated the annual additional mortality, b. The average mortality in 10-year groups was taken as the geometric mean of the constituent 5-year groups. Hayward & Lucerna (1965) give the observed number of deaths of diabetics, the number of years exposed to risk, and the number of deaths expected if the mortality were the same as the population mortality. The

data are given in three groups representing diabetics diagnosed in three quinquennia betw 1945 and 1959. We have added the data in the three groups to obtain a single estimate of additional mortality, b. The values obtained from these two other sources are given in Tabl with our estimates from the current-age groups. Our values are very close to those derived fr

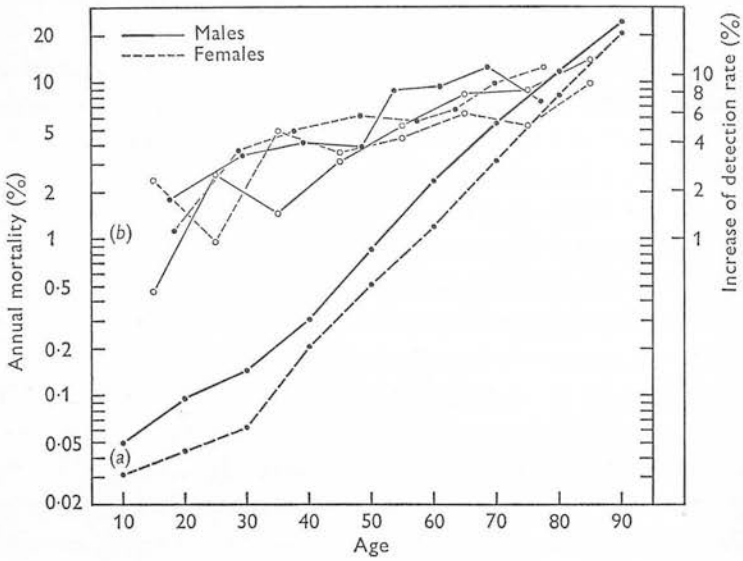

Fig. 12. Annual mortality rates. (a) Population mortality; (b) estimated additional mortality risk to diabetics. The estimates of (b) are upper limits based on the assumption of constant detection rates; full circles from onset-age groups (plotted against mean current age), open circles from current-age groups. The scale on the right shows the annual increase of the detection rate on the alternative assumption of no additional mortality of diabetics.

Table 7. *Additional annual mortality risk* (b) *to diabetics, percentage. Estimates of upper limits from present data compared with estimates from two other sources*

Age group	Present data (current-age groups) Males	Present data (current-age groups) Females	Post (1962) Males	Hayward & Lucerna (1965) Males	Hayward & Lucerna (1965) Females
10–19	0·5	2·4	0·4		
20–29	2·6	1·0	1·1	0·2	0·6
30–39	1·5	4·9	0·9		
40–49	3·1	3·5	2·2	0·6	0·3
50–59	5·3	4·4	4·3	0·7	1·3
60–69	8·5	6·3	8·0	1·1	2·0
70–79	9·0	5·3	—	2·6	3·5
80–89	14·1	9·9	—	4·4	0·4

Post's data, but are considerably higher than those derived from Hayward and Lucerna's d These comparisons are thus inconclusive. The agreement with Post's data shows that our v are not impossibly high, and that the frequency reduction could be due entirely to mort The discrepancy between ours and Hayward and Lucerna's data on the other hand, sug that part of the frequency reduction may be due to other causes.

Detection rate

We now assume that there is no differential mortality of diabetics, and that the frequency reduction is entirely due to an increasing detection rate. In the absence of differential mortality, the annual incidence in each cell of Table 6 estimates the morbidity risk at the corresponding date of diagnosis, and the slopes of the lines in Fig. 9 measure the changes in the detection rates of diabetics in the different age groups. The calculations described in the previous section lead at once to the estimates of the rate of increase of the detection rate. For this purpose the grouping by onset age is appropriate since it gives the morbidity risks at the ages of onset. The constant, k, which was estimated from the regression coefficients, is now the proportionate change of the morbidity risk between one year to the *preceding* year. Thus, if m_y is the morbidity risk in year (date) y, then the morbidity risk in the preceding year is $m_{y-1} = km_y$. The proportionate annual increase of the detection rate between one year and the *following* year is then expressed by

$$(m_y - m_{y-1})/m_{y-1} = (1/k) - 1.$$

The graphs of the onset-age groups in Fig. 12 show the proportionate increase of the detection rate in each age group, when read against the scale on the right. The estimated increase of the detection rate is 1–2 % per annum in the 0–9 onset-age group, and it rises to about 10 % per annum in the 60–69 group.

Independent and direct evidence on changes of the detection rate can be obtained from records of the numbers of patients registered in successive years. For this purpose the numbers registered at the Royal Infirmary Diabetic Department from 1948 to 1968 were obtained. The records of this clinic provided over 70 % of the diabetics in the data (see Table 1) so the numbers registered should give a good indication of any changes of incidence. The population numbers were virtually constant over the period. Taking all ages together there was no change in the numbers of females registered, which varied around a mean of 250 per year. The numbers of males, however, increased fairly regularly from about 125 to about 230 per year, which makes an annual increase of 3 %. This is not nearly enough to account for the frequency reduction which, if due to increase in detection rate, implies an annual increase of about 8 or 10 %.

Hayward & Lucerna (1965) give the age-specific incidences of new cases, registered at a hospital drawing cases from the West Midlands, in three quinquennia, 1945–49, 1950–54, 1955–59. From their figures we have calculated roughly the annual rate of increase between the second and third quinquennia, which corresponds most closely with the period of our data. There was no increase in the incidence of males under the age of 30. In males over 30 the annual rate of increase was about 7 %. Females showed no increase of incidence, except those over 70, in whom the increase was at about the same rate as in the males. These data show much the same picture as ours but the rate of increase was about twice as great.

CONCLUSIONS AND DISCUSSION

The overall prevalence of the ascertained cases of diabetes mellitus in Edinburgh is 0·63 % which is close to the values found in other studies; the mean prevalence found in eight comparable studies summarized by Malins (1968) is 0·68 %. If the observed prevalence in the present study is increased by 5–10 % to allow for the estimated number of cases missed in the recording, the figure becomes between 0·66 and 0·69 %. When the sexes are considered separately we find the overall prevalence not very different – 0·57 % in males and 0·67 % in females. This is in con-

trast with earlier studies where a large excess of women diabetics was found, and it shows a continuation of the trend toward equality that has already been noted (Malins, 1968). Malins in discussing the possible reasons for the changing sex ratio among diabetics, says that the possibility that it is due to a decrease among females rather than an increase among males cannot be ruled out. Our results, however, point more towards an increase in males because the number of new cases recorded annually increased in males but not in females, and the same trend was also observed by Hayward & Lucerna (1965).

The distribution of onset age among living diabetics (Fig. 5) shows nothing unusual. There is a suggestion of bimodality, with a small hump at the age of about 20 and the main peak at about 55–60. The distribution of onset age, however, is not very informative because it depends on three factors, the age-specific morbidity risk, the age-distribution of the population, and the mortality of diabetics. In particular, the fact that very few diabetics have onset after the age of about 80 does not mean that the risk of becoming diabetic after that age is very low; it results simply from the small number of people of that age in the population.

The age-specific morbidity risk (Fig. 10) is a more interesting and informative statistic. In contrast to the distribution of onset age, the morbidity risk does not fall off in the oldest groups; it increases with age up to about 70, after which it may flatten off, but does not decline. Thus the risk of becoming diabetic is highest among the oldest people.

The distribution of onset age has been taken to indicate that virtually all 'potential diabetics' have become manifesting diabetics by the age of about 80. On this basis Post (1962) has concluded that the number of manifesting diabetics found among the children of conjugal diabetics fits the single gene model for the inheritance of diabetes. This, we believe, is an erroneous conclusion, because the morbidity risk shows that old people still have a high risk of becoming diabetic. Post's single gene model would therefore require a larger number of diabetics than is calculated on the assumption that all 'potential' diabetics have become diabetic by the age of about 80.

The possible distinction between early- and late-onset diabetes is another question to which the morbidity risk rather than the distribution of onset-age is relevant. The distributions of onset-age in our data and in some earlier studies (e.g. Simpson, 1964; Malins, 1968) have shown a small hump at about 20, suggestive of bimodality. The morbidity risk shows no clear mode at the age of 20 and it therefore provides no clear evidence for separating early- and late-onset diabetes as distinct entities. There is, however, a discontinuity in the curve, which increases more slowly between 20 and 35 than it does before or after. The shape of the curve, with this discontinuity, is compatible with early- and late-onset diabetes being distinct entities, provided the ages of onset of the two overlap between about 20 and 40. Nearly all cases with onset before 20 would then be of the juvenile type, and nearly all cases after about 40 of the adult type, while cases with onset at about 30 would be about half of each type. This interpretation fits the clinical picture well, but the evidence for it from the morbidity risks is not strong.

If the annual morbidity risk is cumulated year by year, the summation up to any particular age gives the potential prevalence of that age (Fig. 11). The potential prevalence increases with age faster than the actual prevalence, until at the age of 80 it is about eight times as great. The difference between the potential and actual prevalence can be due to one or both of two causes: mortality of diabetics and increasing morbidity risks. The cumulation of the annual morbidity risks gives the prevalence expected if the survival rate of diabetics is the same as that of non-

diabetics. So a higher mortality of diabetics will result in an actual prevalence below the potential. The morbidity risks from which the potential prevalence is calculated are those at the time of the study, whereas the actual prevalence reflects the morbidity risks in the past. Thus if the morbidity risks are higher now than they were in the past, the actual prevalence will be lower than the potential prevalence. The potential prevalence is therefore interesting in showing what the prevalence of diabetes may become in the future, if mortality can be reduced to the level of non-diabetics and if the morbidity risk remains at its present level. In these circumstances we can expect the number of diabetics to rise toward double the present number in people over the age of about 40. It is, however, probably not realistic to expect the actual prevalence to increase to the level of the potential prevalence in the older age groups – an eight-fold increase in people over 80 – for the following reason. Among the older diabetics there are many who are referred to the clinic from hospital wards which they have entered for some other illness. These people have therefore been recognized as diabetic as a consequence of having some other illness and their mortality is not likely to be much reduced by improved treatment of diabetes.

The difference between the potential and the actual prevalence appears in another form which we have referred to as the 'frequency reduction'. The frequency of diabetics in the current population becomes progressively reduced with increasing duration of the disease and consequently with earlier date of diagnosis. In other words there are fewer diabetics who were diagnosed in the past than would be expected from the current morbidity risks. From the rate at which the frequency becomes reduced we can estimate the rate of mortality or the rate of increase of the morbidity risk, but we cannot distinguish between these as causes of the frequency reduction and of the difference between the potential and the actual prevalence. Assuming that mortality is the cause, we find the additional mortality risk to diabetics is about 1 or 2 % per annum at the age of about 20 and rises to about 10 % at the age of 80. The comparable population mortality is about 0·065 % at age 20 and about 10 % at age 80. Thus at age 20 the estimated mortality of diabetics is 20 times the population mortality, and at age 80 it is twice the population mortality. Comparison of these estimates with direct estimates of mortality based on two follow-up studies of diabetics shows that our estimates are very close to those of the earlier study (Post, 1962; data from the Joslin Clinic records), but are higher than those of the later study (Hayward & Lucerna, 1965; data from the Birmingham General Hospital between 1945 and 1959). It seems likely, therefore, that mortality is not the sole cause of the frequency reduction and of the difference between the potential and the actual prevalence.

If increasing morbidity risk is the cause of the frequency reduction, rather than mortality, the rate of increase in both sexes would have to be about 1 or 2 % per annum in the youngest age groups, rising to 8 or 10 % per annum in the oldest groups. So high a rate of increase seems unlikely because the number of registrations of new patients over a period of 20 years showed an increase of only 3 % per annum in the number of males and no increase at all in females. It seems probable therefore, that increasing morbidity risk has contributed only a little to the frequency reduction and that the estimates of mortality derived from the frequency reduction are consequently not very much too high. The only way to distinguish critically between mortality and increasing morbidity risk would be to make an identical study after the lapse of some years. This would provide estimates of the age-specific morbidity risks at two different dates.

Any increase of the morbidity risk that has taken place in the past or may take place in the future could be either an increase of the true incidence of the disease or an increase in the proportion of diabetics who are known to be diabetic through diagnosis. It is well known from population surveys that about as many new, previously undetected, cases are found as there are known diagnosed cases. If the true prevalence remains constant – i.e. the total of undetected and known cases – then an increase of the detection rate would lead to a reduction of the number of new cases found in such a survey. Would such a reduction be detectable over a reasonable period of time? With the proportion of undetected cases being about 0·5, an increase of 3 % in the observed morbidity risk would result from a 3 % reduction in the proportion of undetected cases. If the proportion of undetected cases decreased continuously by 3 % per annum the proportion of undetected cases would be halved after 23 years; or after 10 years it would be reduced from 50 to 37 %. Thus a period of 10–20 years between surveys might well be sufficient to detect the change. Malins (1968) listed the results of eight such surveys with publication dates between 1947 and 1964; the later surveys, however, do not tend to have a lower proportion of new cases. If the detection rate differs between localities and times, but the true prevalence is the same, there would be a negative correlation between the frequency of known cases and the frequency of new cases in such surveys. Conversely, if the detection rates are the same but the true prevalence differs, there would be a positive correlation. The correlation in the surveys listed by Malins is $-0{\cdot}36$, but it is not significantly different from zero. Though inconclusive, this line of evidence is suggestive of a constant true prevalence and a variable detection rate. The present study, because it deals only with known diagnosed cases, cannot throw any light on this problem, which will only be solved by further surveys in which the unknown cases are detected.

SUMMARY

1. Records of current age and onset age of known diabetics resident in Edinburgh and alive at 1 January 1968 were obtained. Ascertainment was estimated to be between 90 and 95 % complete.

2. The overall prevalence was 0·57 % in males and 0·67 % in females.

3. The age-specific morbidity risks were estimated by a new method which uses the information from all living diabetics by relating the frequency to the duration of the disease.

4. The morbidity risk increases continuously with age and reaches 2 % per annum at the age of 70, after which it levels off but does not decline.

5. Cumulation of the annual morbidity risks leads to estimates of the 'potential prevalence' at successive ages. This is the prevalence expected if the mortality of diabetics was the same as that of the non-diabetics and if the morbidity risks were the same as they are now. The potential prevalence increases with age faster than the actual prevalence; at 40 it is about twice as great and at 80 about eight times.

6. The difference between the actual and the potential prevalence may be due to high mortality of diabetics or to the morbidity risk increasing with time, or to both. By analysis of the frequency of diabetics in relation to the duration of the disease and the date of diagnosis estimates were made of the rate of mortality or of the rate of increase of the morbidity risk.

7. Assuming constant morbidity risk, the additional annual mortality risk to diabetics is 1–2 % at age 10, rising to 20 % at age 80. Relative to the population, the mortality is 20 times at age 20 and 2 times at age 80.

8. Assuming no additional mortality, the morbidity risk would have to have increased by 1-2% per annum at age 10 and 8–10% per annum at age 60 to account for the difference between the actual and the potential prevalence. The number of registrations at the Clinic showed an increase of only 3% per annum in males and no increase in females.

We are greatly indebted to Miss J. Henry, B.Sc. who was largely responsible for the collection of the data; to the Records Officers and physicians in all Edinburgh Hospitals; to Mr Robert McLeod and his staff in the Office of the Registrar General for Scotland; and in particular to all the General Practitioners in Edinburgh whose help and co-operation were essential to the study. We also gratefully acknowledge financial support from the British Diabetes Society and Pfizer Ltd.

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Recurrence Risks for Multifactorial Inheritance

CHARLES SMITH[1]

The heritability of liability model [1] has provided a useful tool for summarizing data on relatives for many familial diseases. Edwards [2], using tetrachoric functions, and Smith [3], using numerical integration of the normal curve, have developed the model further, deriving unbiased risks to relatives and concordance rates in monozygotic twins. The risks derived are the mean risks for relatives of affected individuals. These risks, however, may be modified if further information on other family members (both affected and unaffected) is available. Moreover, since the information on different relatives is not independent, its combination is not straightforward.

In this paper a method is described to derive the recurrence risk of a condition with multifactorial inheritance in any family presented. The contributions of information about affected first-, second-, and third-degree relatives and about unaffected relatives are considered. Confidence limits on the risk estimates can also be derived. The methods can handle differences in frequency between sexes, variable onset age, and other factors likely to be met in practice.

Some results are presented, but, because of the variety of possibilities for family history and other variables, it is proposed that a computer be used to estimate the risk for each family specified. The methods are given in some detail to allow the user to develop his own computer program. Another important use for these methods is to generate data for multifactorial inheritance on familial frequency and on segregation frequencies for families [4]. Hence they provide a method for iterative solution for a maximum-likelihood fit by the multifactorial model to data on genetic disease [5], and thus for comparing the fit of multifactorial and other modes of inheritance to data on genetic disease [6].

Curnow [7] has recently developed mathematical expressions for the recurrence risks in sibships, assuming multifactorial inheritance. The expressions for the recurrence risks involve single integrals with the integrands composed of a normal frequency function and the product of certain normal distribution functions. Thus far, expressions are available for parents, twins, and sibships with up to four children. The recurrence risks obtained by Curnow are essentially the same as the results presented in this paper.

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MODELS AND METHODS

The threshold. The multifactorial model [1] assumes an underlying continuous liability to a disease, the liability being the sum of many genetic and environmental effects, and thus being normally distributed. The disease becomes manifest if an individual's liability exceeds a critical threshold level. The abrupt threshold model has been criticized for being biologically unrealistic [2]. However, it can be shown that the threshold model is identical to a normally distributed genetic liability with a cumulative normal risk function. In figure 1, the standardized phenotypic distribution of liability is shown with

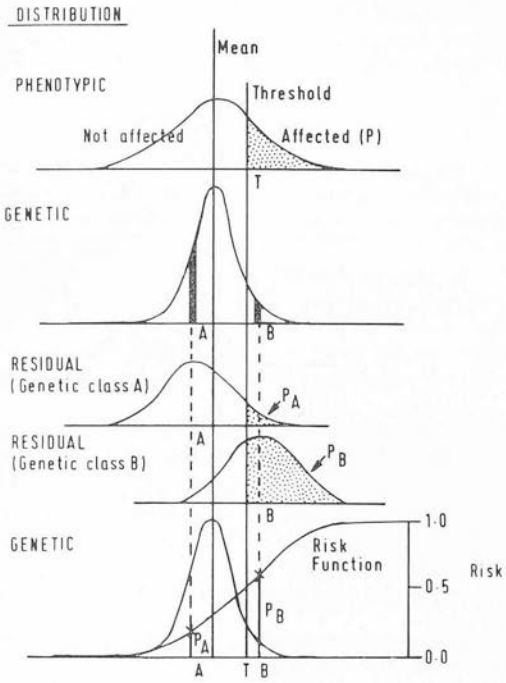

FIG. 1.—Diagram showing that the threshold model corresponds to a normally distributed genetic liability with a cumulative normal risk function.

the proportion affected (P) defining the threshold point and the mean of the distribution. Below it the genetic distribution of liability is shown, with the same mean but with a smaller variance (h^2). Two genetic classes A and B are shown with their residual (environmental) distributions drawn below, the variance being $(1 - h^2)$ and with P_A and P_B, respectively, the proportions in the genetic classes exceeding the threshold T. Finally, redrawing the genetic distribution and plotting the risks P_A and P_B (and similarly for other genetic classes), it can be seen that the original threshold model implies a normal genetic distribution with a cumulative normal risk function rising to a risk of unity at the limit. Algebraic proofs of this property of the threshold model have been given recently by Mendell and Elston [8] and by Curnow [7].

Recurrence risks. The method to estimate recurrence risks depends on partitioning the genetic distribution of liability into a number of classes, estimating the risk to individuals

in each class (and the risks to their relatives), and numerically integrating over all classes [3]. The details of the method are given below and in figure 2 for a sibship family.

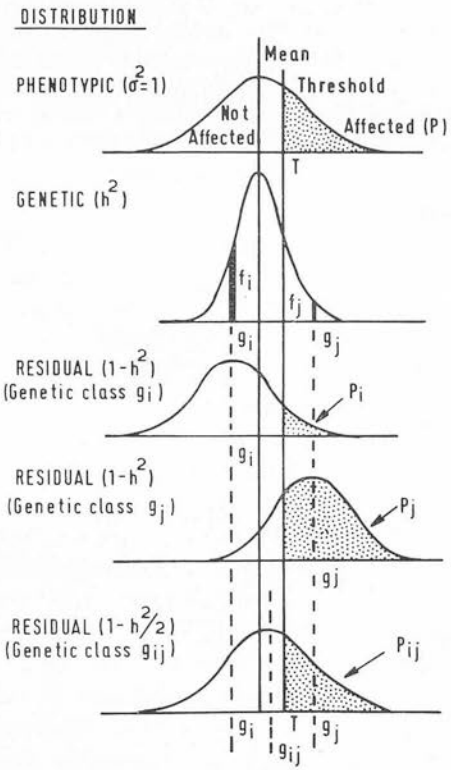

FIG. 2.—Diagram showing parental and offspring genetic classes and the corresponding risks

Assume an underlying standardized normal phenotypic distribution of liability to the disease. The corresponding genetic distribution (variance $= h^2$) can be divided into an ordered series of genetic classes, each with a known frequency. In figure 2, a genetic class g_i with frequency f_i is shown for the father, and similarly for the mother (j). It is assumed that the genetic values of the parents g_i and g_j are independent. The mean genetic value of the offspring g_{ij} is then $(g_i + g_j)/2$, with a residual genetic variance $h^2/2$ about this mean. Since the genetic value g and the residual variance VR are known, the deviation from the threshold T is $(T - g)/\sqrt{VR}$, and the proportion P of a class exceeding the threshold can be derived giving P_i and P_j for the father and mother, and P_{ij} for an offspring. The recurrence risk for a given sibship can then be found by summing over all possible combinations of the i and j parental classes. For example, in a sibship with a normal father, an affected mother, and with s children, r of whom are affected, the recurrence risk is:

$$\sum_i \sum_j Q_{ij} P_{ij} / \sum_i \sum_j Q_{ij},$$

where

$$Q_{ij} = f_i f_j (1 - P_i)\, P_j (1 - P_{ij})^{s-r} P_{ij}^{r}.$$

Expressions of this form are readily evaluated by computer [3], given the heritability

(h^2) and the population frequency P. Subdivision of the distributions into 21 genetic classes has provided an accuracy to 0.1% in calculating the risks.

Other relatives. The extension to second- and third-degree relatives is theoretically similar. Additional genetic distributions must be generated for all original members of independent branches of the family. Further, for any intermediate family member with offspring, a genetic distribution (with the appropriate variance) must be generated, since his disease status gives information about his own genotype and hence about the mean genotype of his offspring.

Confidence intervals for risks. A recurrence risk estimated by the above methods will be the mean for the family type generated, and will have a variance about this mean. Since the information on a family is usually limited, the confidence intervals on the risk estimated may be quite large. The confidence intervals can be estimated simultaneously with the recurrence risk by accumulating the square terms

$$\sum_i \sum_j Q_{ij} P_{ij}^2,$$

and finding the variance and hence the confidence limits in the usual fashion.

Approximate recurrence risks. If separate genetic distributions must be generated for several members of the family, then the amount of computing involved may be increased many-fold and may become prohibitive. In such cases only an approximate solution is possible. Three possible simplifications have been considered: (1) to omit unaffected relatives, (2) to omit second- and third-degree relatives, or (3) to generate distributions only for the two parents of the sibship at risk and to treat others in the family through their genetic relationship with the father or the mother. The third alternative restricts the amount of computing required and makes the other two simplifications unnecessary.

Details for alternative (3) are given in the Appendix so that the user may write his own computer program to estimate recurrence risks in complex families. Alternatively, a program (RISKMF) is available on request from this department. The same procedure can be further developed to cover diseases having different frequencies in the sexes, a changing frequency with age, and a variable heritability depending on sex and age (see Appendix).

RESULTS

For any given sibship, the exact recurrence risks are derived quickly by the methods described. Results are shown in table 1 for a variety of sibships with zero, one, or two affected parents, and for various levels of heritability and population frequency. These can be used directly in genetic counseling. If the heritability is unknown, the recurrence risks for a heritability of 100% can be used as the maximum risk with multifactorial inheritance for the population frequency specified. In much of the table, the risks are not high; only when several individuals are affected, heritability is high, or the disease is fairly common, do the recurrence risks become large.

The pattern of risks in table 1 is illustrated in figure 3 for 10 sibships (heritability = 80%). As before, the risks are linear functions of the population frequency, if both are measured on a logarithmic scale. This allows simple interpolation from graphs (or tables) to different population frequencies. The risks at lower levels of heritability show a pattern similar to figure 3, but with lower risks throughout. It is also clear from figure 3 that omitting unaffected relatives will result in too high a risk figure, especially if the population frequency is high.

TABLE 1

RECURRENCE RISKS (× 1,000) IN SIBSHIPS

POPULATION FREQUENCY (%)	HERITABILITY (%)	NO. NORMAL SIBS	NO. AFFECTED PARENTS								
			0			1			2		
			NO. AFFECTED SIBS								
			0	1	2	0	1	2	0	1	2
10.0	100*	0	055*	165	244	283	409	493	731	751	769
		1	049	149	230	234	351	433	678	695	712
		2	043	136	210	198	306	387	641	657	672
	80	0	064	165	252	235	347	432	557	607	649
		1	057	148	228	200	302	382	493	543	585
		2	052	134	208	175	267	342	444	493	535
	50	0	080	151	220	178	257	326	335	401	457
		1	074	139	203	160	233	297	301	363	417
		2	068	129	188	147	213	273	275	332	383
	20	0	093	123	154	129	161	193	174	207	240
		1	089	119	148	124	155	186	167	199	230
		2	087	115	143	120	149	179	160	191	221
1.0	100*	0	007	073	144	112	240	338	633	649	666
		1	007	067	135	096	209	301	606	617	630
		2	006	062	127	084	185	271	588	597	606
	80	0	008	065	142	083	185	278	409	466	516
		1	008	060	130	074	164	248	370	423	470
		2	008	055	120	067	148	224	338	389	434
	50	0	009	039	084	043	093	151	146	206	261
		1	009	037	079	040	087	141	135	191	245
		2	009	035	075	038	082	132	127	178	229
0.1	100*	0	001	038	108	049	156	257	620	629	640
		1	001	035	100	044	137	230	604	612	620
		2	001	033	093	040	123	207	592	599	605
	80	0	001	025	082	029	098	179	317	374	424
		1	001	024	076	027	089	163	290	345	392
		2	001	022	071	025	082	149	268	320	366
	50	0	001	010	032	010	034	069	066	109	153
		1	001	010	031	010	032	066	063	104	145
		2	001	009	030	010	031	063	060	099	139

* Evaluated for $h^2 = 99\%$.

The recurrence risk increases substantially as additional affected individuals appear in the sibship. However, it does not seem possible to generalize this change of risk from the empirical results, since it depends on the composition of the sibship, the heritability, and the population frequency. One interesting result is that, with two parents affected, the risk is much higher than for two affected sibs (or one parent and one sib). This is because the parents are genetically independent and contribute independent information for assessing risks to their children.

The confidence limits on the recurrence risks depend almost entirely on the level of risk. Thus, if the same risk is maintained but many relatives are con-

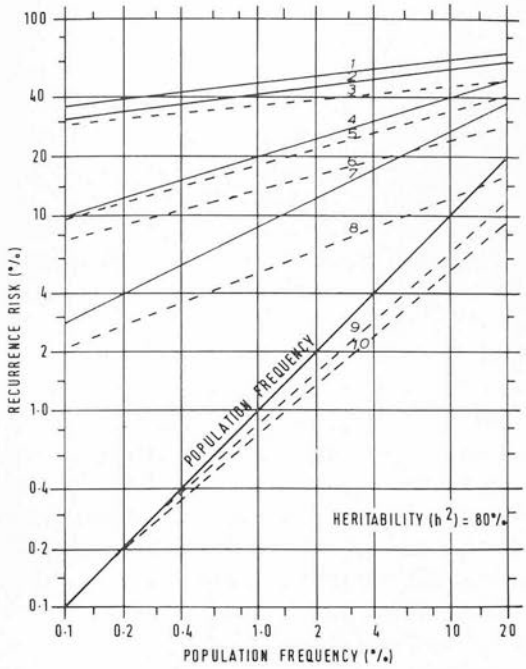

FIG. 3.—Recurrence risks in a variety of sibships (broken lines include normal relatives). Sibships: *1* = 2 parents, 1 sib affected; *2* = 2 parents affected; *3* = 2 parents, 1 sib affected, 3 sibs normal; *4* = 2 sibs affected or 1 parent, 1 sib affected; *5* = 1 parent, 1 sib affected, 1 parent normal; *6* = 1 parent, 1 sib affected, 1 parent, 3 sibs normal; *7* = 1 sib affected or 1 parent affected; *8* = 1 sib affected, parents, 3 sibs normal; *9* = parents normal; and *10* = parents, 2 sibs normal.

sidered, the confidence limits are only slightly reduced. The upper 95% confidence limits are about four times the risk if the risk is low (under 1%), falling to about twice the risk if the risk is high (over 20%). The lower confidence limits are usually near zero unless the risk is very high.

Inclusion of second- and third-degree relatives does affect the recurrence risks in the family. The exact risks were calculated when only a few distributions had to be generated; otherwise the approximate method was used because the amount of computing becomes prohibitive. Where comparisons between the methods were possible, the approximations were good (to within 1%–2% of the exact risk). Some results for second- and third-degree relatives are shown in figure 4, using the approximate method for estimating the risks. Each affected relative adds further to the recurrence risk. As a rough guide, two affected second-degree relatives or several third-degree relatives may be taken as equivalent to one affected first-degree relative. As before, omission of unaffected second- and third-degree relatives gives risks which are somewhat too high, but even when these unaffected relatives are numerous, the effect is not very large.

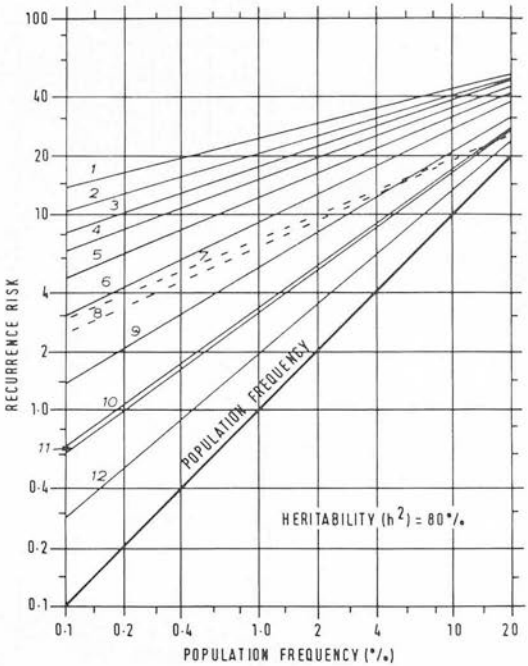

FIG. 4.—Recurrence risks for families with information on second and third degree relatives. Family: *1* = 1 sib, 1 paternal uncle, 1 maternal uncle affected; *2* = 2 sibs affected or 1 sib, 1 paternal uncles affected; *3* = 1 sib, 1 uncle, 1 cousin affected; *4* = 1 sib, 1 uncle affected; *5* = 1 sib, 1 cousin affected; *6* = 1 sib affected; *7* = 1 sib affected, 5 uncles, 10 cousins normal; *8* = 1 sib affected, 2 sibs normal; *9* = 1 uncle, 1 cousin affected; *10* = 1 uncle affected; *11* = 2 cousins affected; and *12* = 1 cousin affected.

DISCUSSION

The methods described allow us to calculate exact recurrence risks in sibships and in small families, and to estimate approximate risks in large or complex families. The results presented in table 1 and in figures 3 and 4 cover some simple cases and may be a useful guide in genetic counseling. However, in practice, the wide range of possibilities in family history, population frequency, sex frequency, heritability, onset age, and severity would require a very extensive set of tables. As an alternative, it is proposed that the computer be used to calculate the risk for the specific family and disease involved. The methods are described in detail and the user can write his own program (or obtain the version RISKMF available from this department) for estimating risks. With on-line computing facilities becoming generally available, this approach becomes feasible and preferable because of its scope and flexibility.

It may be argued that exact recurrence risks are neither needed nor justified in practice. For genetic counseling, an approximate level of risk is usually sufficient. Moreover, the exact risk figure may be misleading because there will be real

differences in risk among families with the same family history and the confidence limits on the risk estimates will be wide. The suitability of the multifactorial model may also be questioned, with its assumption of additive genetic effects, normality, and the absence of familial environmental effects. Thus the model, and the recurrence risks derived from it, should be regarded as useful in analysis and for predictions on quasi-continuous genetic disorders, rather than as proof of the true genetic basis or of the exact risks involved. With multifactorial inheritance, the risks involved are usually low unless several relatives are affected or the frequency of the condition is high (over 2%). Thus the risk estimates may be most useful for the more common diseases with variable age of onset.

Two other methods of estimating recurrence risks should be mentioned. Morton [9] has proposed that where the risks are variable between sibships, the distribution of risks may be well represented by a beta function. The parameters of the beta function can be estimated as $A = (1 - P_R)/(1 - P)$ and $B = AP$, where P is the population frequency and P_R is the frequency in relatives of affected individuals. The recurrence risk, given s sibs with r affected, is then $(B + r)/(A + s)$. To take account of the disease status of the parents, the appropriate values of P_R for zero, one, and two affected parents would be required. The recurrence risk estimated by this procedure was compared with the risk assuming multifactorial inheritance for a range of sibships, heritabilities, and frequencies. In general, the agreement with the multifactorial risk was quite good, as shown by the examples given in table 2. However, use of this approximation (in its present form) would

TABLE 2

RECURRENCE RISKS FOR MULTIFACTORIAL INHERITANCE IN SIBSHIPS OF SIZE 4 AND RISK ESTIMATES BY THE BETA FUNCTION APPROXIMATION*

No. in Sibship	No. Affected	Multifactorial Risk† (%)	Beta Function Risk Estimate† (%)	Multifactorial Risk‡ (%)	Beta Function Risk Estimate‡ (%)
4	0	11	11	2	2
4	1	17	17	8	8
4	2	23	23	15	14
4	3	29	29	23	20
4	4	36	34	32	26

* See [9].
† Population frequency, 1.0%; heritability, 50%; two parents affected.
‡ Population frequency, 0.1%; heritability, 80%; one parent affected.

be restricted to sibships, and good empirical estimates of recurrence risks in sibships with one affected and with zero, one, and two affected parents would be required.

Another method to estimate recurrence risks is through the genetic selection index [10]. This procedure derives a multiple regression equation (or index) which maximizes the correlation between the genetic liability of the person at risk

and the observed disease status of his relatives. This method provides good approximations of the risk for many situations (Smith and Mayo, unpublished), but in some extreme cases (e.g., families with none affected), the divergence is quite large, and the method is being investigated further. The advantage of the selection index approach is that information on physiological or other measurements correlated with liability could be included in estimating risks.

SUMMARY

The abrupt threshold model of liability to genetic disease [1] is shown to correspond to a normal genetic distribution of liability with a cumulative normal risk function. A method for estimating recurrence risks for any family history in conditions with multifactorial inheritance is described. The method depends on partitioning the genetic distribution of liability into a number of classes, estimating the risk (and the risk to relatives) in each class, and numerically integrating over all classes. A table of risks is presented for a variety of possible sibships. The effect of inclusion of second- and third-degree relatives is also considered. To reduce the amount of computing required in large or complex families, an approximate method is proposed. This method is described in detail (Appendix) so that the user may write his own computer program to estimate recurrence risks for any familial situation.

APPENDIX

APPROXIMATION OF RECURRENCE RISKS

The amount of computing to estimate the risks in a family is proportional to the nth power of the number of genetic classes, where n is the number of separate distributions generated in the family. For large or complex families, the computing time becomes prohibitive. To reduce this time and to formalize the computation procedure, an approximate method was adopted. This generates only two genetic distributions, one for the father and one for the mother of the sibship at risk, and treats other members of the family through their genetic relationship with the father or the mother. This procedure gives the exact risks for sibships and provides good approximate risks for families, with second- and third-degree relatives considered. The pedigree is thus of the form shown in figure A1, with *1* representing the father, *5* and *6* the second- and third-degree paternal

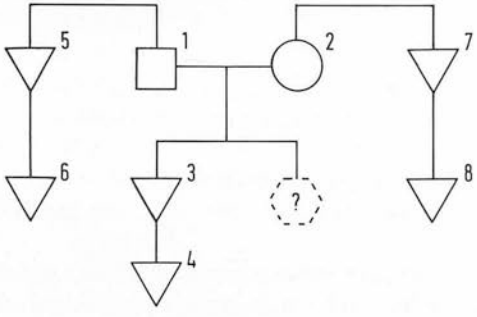

FIG. A1

relatives (*2*, *7*, and *8* for the maternal side), *3* representing sibs, and *4* the children of sibs of the individual at risk.

The formulas required for estimating the proportions of different relatives affected are given in table A1. It is assumed that there is no sex difference in frequency, and that

TABLE A1

FORMULAS FOR ESTIMATING RECURRENCE RISKS FOR PARENTAL CLASS (*ij*)

CLASS OF RELATIVE	CLASS (k)	DEVIATION* (d_k)	RESIDUAL VARIANCE (σ_k)	PROPORTION AFFECTED (P_k)	SAMPLE FAMILY DATA: No. (n_k)	SAMPLE FAMILY DATA: No. Affected (a_k)
Father	1	$T - g_i$	$(1 - h^2)$	P_1	1	0
Mother	2	$T - g_j$	$(1 - h^2)$	P_2	1	1
Sibs	3	$T - \frac{1}{2}(g_i + g_j)$	$(1 - \frac{1}{2}h^2)$	P_3	4	1
Sib's children ..	4	$T - \frac{1}{4}(g_i + g_j)$	$(1 - \frac{1}{8}h^2)$	P_4	0	0
Paternal 2d degree	5	$T - \frac{1}{2}g_i$	$(1 - \frac{1}{4}h^2)$	P_5	3	1
Paternal 3d degree	6	$T - \frac{1}{4}g_i$	$(1 - \frac{1}{16}h^2)$	P_6	6	0
Maternal 2d degree	7	$T - \frac{1}{2}g_j$	$(1 - \frac{1}{4}h^2)$	P_7	1	0
Maternal 3d degree	8	$T - \frac{1}{4}g_j$	$(1 - \frac{1}{16}h^2)$	P_8	4	0

*For details, see text.

the condition is manifest at birth. Given the population frequency P, the threshold point T is calculated from the normal curve. The ith paternal genetic class g_i has a frequency f_i and a mean which is $d = (T - g_i)$ phenotypic standard deviation units below the threshold, and similarly for the mother and for the other classes of relatives (through their relationship with the parents). The proportion affected (P_k) for each class of relative is then the probability of a normal deviate greater than d_k/σ_k, where σ_k^2 is the residual variance in the relative class. The recurrence risk is then:

$$\sum_i \sum_j Q_{ij} P_3 / \sum_i \sum_j Q_{ij}$$

where

$$Q_{ij} = f_i f_j \prod_{k=1}^{8} (1 - P_k)^{(n_k - a_k)} P_k^{a_k},$$

with a_k out of n_k affected in relative class k. For example, in the sample family shown in table A1, for a condition with a heritability of 80% and a population frequency of 1%, the estimated recurrence risk is 20%, with 41% as the upper 95% confidence limit. Computing time with 21 genetic classes in the parental distributions was less than one minute. Standard computing routines are available for the necessary operations on the normal curve.

The same methods can easily be extended to cover more complex situations—specifically, where there is a different frequency in the sexes, where the age of onset is variable and the frequency increases with age, and where the heritability may depend on the sex and age class. Relatives may then have to be treated separately, or in subgroups, to take into consideration their sex and age class. It can be shown for genetic class i of father F and genetic class j of mother M, that the standardized deviation in liability for a relative in sex class s and age class t from the threshold T_{st} for the st class is:

$$[T_{st} - (b_{kF}g_i + b_{kM}g_j)]/\sqrt{1 - R^2h_{st}^2},$$

where h_{st}^2 is the heritability in the st class, b_{kF} is the regression on father's genotype of the genotype of the relative class k being considered (and similarly for b_{kM}), and R is the genetic relationship of the relative class k with the mean of the parents of the individual at risk. The proportion affected for each parental (ij) and risk class (st) can then be estimated and the overall recurrence risks computed in the usual way. Alternatively, the liability of the individual at risk can be evaluated, and the risk at different ages (or the lifetime risk) can be estimated.

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INDIVIDUALS AT RISK IN FAMILIES WITH GENETIC DISEASE

BY

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Individuals at Risk in Families with Genetic Disease

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With the control of many infectious diseases and improvement in medical care, there have been dramatic changes in the pattern of mortality and morbidity in society. As a result, genetic diseases have been increased in their relative importance in the population. For example, Roberts, Chavez, and Court (1970) have found in hospital deaths among children that genetic conditions were directly or indirectly involved in over 40% of cases. Since the liability to genetic disease is inherited and intrinsic to the individual and to his family, rather than acquired or extrinsic as for non-genetic diseases, quite different systems of prevention and control are required. To some extent, these systems will require new departures from the established methods of medical practice.

Until recently the main application of medical genetics has been in counselling the parents of affected children. The possibility of extending the scope for application has been examined recently. Fraser and Motulsky (1968) estimated what proportion of cases of genetic disease might be prevented, and Smith (1970) has examined the value of different routes of prevention and the possibility of a genetic register system. McKusick (1969) has also discussed a medical record system for family follow-up in the detection and early treatment of cases of genetic disease. In a previous study (Emery and Smith, 1970), it was shown that only a small proportion of individuals 'at risk' of having affected children were in fact referred specifically for genetic counselling. Many were referred only after the birth of an affected child which otherwise could have been prevented. These results confirmed the need for a genetic register system in preventing genetic disease.

The object of this paper is to outline our experiences in recording and storing relevant data on families with genetic disease and in assessing risks to various members of the family. Details of the procedure used and a summary and interpretation of the data collected so far are presented.

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Methods and Material

Assessment of Risks. Roberts (1962) grouped genetic diseases into those with a high risk of recurrence (greater than 1 in 10) and those with a low risk of recurrence (less than 1 in 20). This convention is now generally accepted and is adopted here. Thus, an individual was defined to be 'at risk' if he had a greater than 10% risk (1) of becoming affected or (2) of having affected children or children who will be 'at risk'. Those unlikely to have children in the future either due to their disease condition or due to their age (over 40 years) are excluded from category 2.

The methods of assessing the risks to family members are best described from some examples (Fig. 1).

In family A with an autosomal recessive (AR) condition, the mother was the first contact. She came for counselling *retrospectively*, ie, after the birth of her

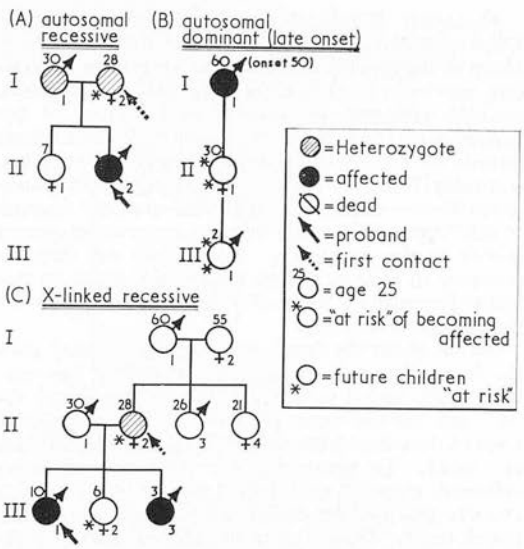

FIG. 1. Pedigrees illustrating the methods of assessing risks (see text).

affected son, the proband. The risk of the next child being affected is high (25%) and this risk is allocated to the mother. There are no others at risk in the family.

In family B, suppose the autosomal dominant (AD) condition is Huntington's chorea. From a cumulative graph by onset age of cases of this disease (Emery, 1969), the risks of becoming affected are about 40% for the mother and 20% for the son; the risks of having children with the abnormal gene are then 20% and 10% respectively, so both are deemed to be also at risk of having children who may become affected. Since the mother (II.1) has been known to be at risk since her father's diagnosis some 10 years ago the birth of her 'at risk' son could have been prevented.

A more complex case (family C) is illustrated for an X-linked recessive (XR) condition, eg, Duchenne muscular dystrophy. With two affected sons, the mother is a definite carrier. The risks of her next having an affected boy or carrier daughter are each 25%. These risks have been summed in the XR conditions so that the combined risk in this case is taken as 50%. Similarly the daughter (III.2) is taken to be at risk since she has a 50% chance of being a carrier. Assuming the proband was diagnosed early, the birth of his affected brother (III.3) might have been prevented. Is the contact's sister (II.4) at risk? The probability that the grandmother (I.2) is a carrier is 33%, so the sister (II.4) has a 17% chance of being a carrier. Her risk of having an affected son *or* a carrier daughter is thus 18%. Further information on her carrier status could be obtained by a serum creatine kinase test (eg, Fig. 2) leading to a more precise estimate of her risk (see Emery, 1969).

Material. The families studied were from either the Edinburgh or the Manchester region during 1965–70. Many of the families were referred for genetic counselling, but some were seen for other reasons: diagnosis, teaching purposes, or research work. Some of the families were traced from hospital or health department records or through members of certain societies (eg, Muscular Dystrophy Group). The kinds and frequency of the diseases studied thus reflect the work and interests of this Department rather than the spectrum of genetic disease in the population. No attempt was made to ascertain all cases of genetic disease in a region so that this is essentially a study of ascertained families rather than a population study.

Details about the family were usually obtained from the first person to be seen in the family, the first contact. This verbal report about the pedigree and the ages and disease status of family members provided most of the information on which the following analyses are based. To systematize the form of information collected, a special record card was designed (Fig. 2) and this was used for coding and punching the data on punch cards. Details on name, address, general practitioner, etc were recorded. At examination the clinician gave a summary of the clinical report and findings, filled in other relevant details and circled the appropriate responses. Each family was allocated a separate family number. Separate cards were completed for any further members of the family who were judged to be at risk. A special two-part disease code was developed but, to conform with common usage, the International Disease Classification (with an additional 5th digit to allow for discrimination between different genetic conditions) will be used in future. A second disease category was available, to record associations of different diseases in one family. The remainder of the first side of the card dealt with details on sex, dates of birth, details of the visit, and the mode of referral.

On the reverse side of the card (Fig. 2 below), the pedigree and further details were recorded as shown.

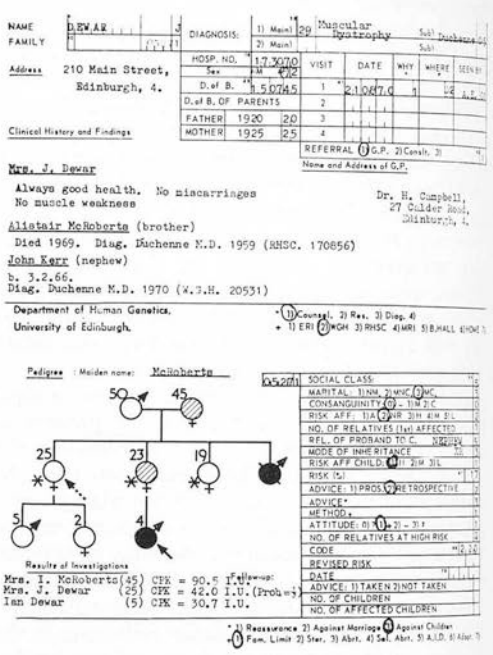

FIG. 2. Example of a completed family record card. The details are purely fictitious and are used only for illustration.

These included social class (5 groups); marital status (not married, married with no children, married with children); consanguinity (none, mild, close); status (affected, no risk, high risk, medium risk, low risk); number of first-degree relatives affected; relationship of the proband; mode of inheritance; risk of having an affected child (high, medium, low—and as a percentage); and whether the record was made before (prospective) or after (retrospective) the birth of an affected or 'at risk' child to the individual concerned.

If the person was counselled, the advice given was noted, together with any method of family limitation advised and the person's attitude to the counselling. Finally, for the first contact in the family, the number and relationship codes of relatives at risk were recorded.

Further columns were left for any revision of the risks and for details of follow-up.

The information obtained on the families was not always complete because the cards for relatives at risk were prepared from the information given by the first contact at interview. Moreover some of the families were ascertained before the present recording scheme was developed, so past files had to be used and these were often incomplete. This may have led to some underestimation of the numbers affected and at risk, for only recorded information could be used. For analysis on a particular topic all data available on that topic were used. Almost all families ascertained were included in the analysis. These included conditions that were either not serious or not genetic or whose nature was not resolved, and form the 'other' category in Table I. The term 'multifactorial inheritance' in Table I refers to familial diseases which are possibly due to many loci plus the effects of environment and include some of the congenital malformations, diabetes mellitus, and schizophrenia (Carter, 1969).

Results

Families. Reasons for ascertainment and other details about the families studied are given in the series of histograms in Fig. 3. Over half of the families were referred for genetic counselling and the rest mainly for diagnosis or research. The chief source of families referred was the hospital consultant who contributed almost two thirds of the total. Most of the remainder were referred directly by the family's general practitioner. The distribution of the families by social class, though not directly comparable to the distribution in the

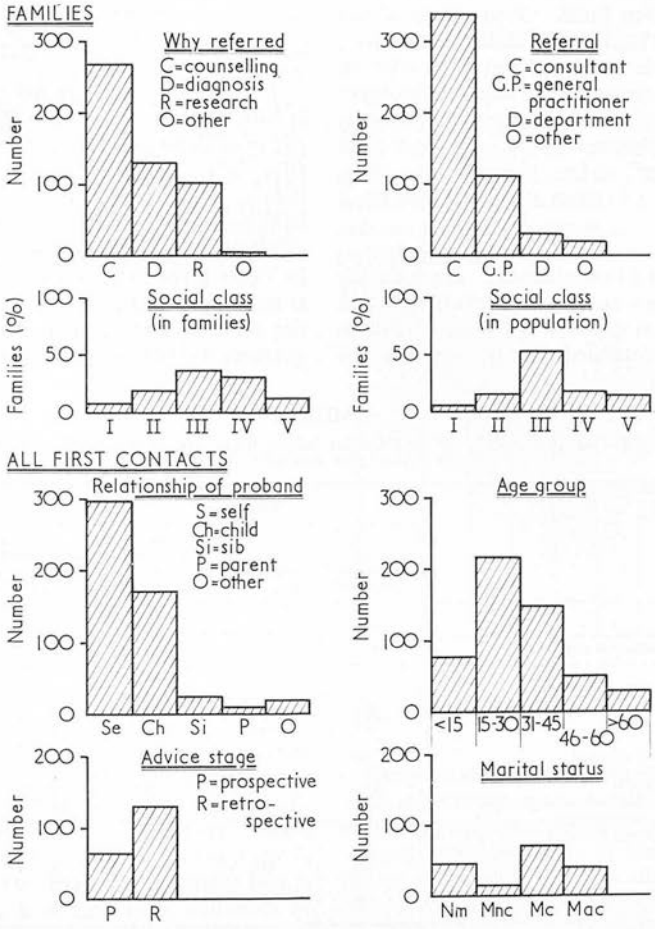

FIG. 3. Distributions of families and of first contacts (for serious genetic conditions) by various classifications of the data.

population (1961 Census) because of age and other differences, shows an apparent excess of families in social classes 1 and 4 and a corresponding deficit in class 3. However all social classes are well represented in the families ascertained.

First Contacts. The remaining histograms in Fig. 3 refer specifically to the first contact in each family. Most of these were either the affected proband (usually in families referred for diagnosis or research) or the proband was the child of the first contact (usually in families referred for genetic counselling). This indicated that few other relatives in affected families were referred about their possible risk (*cf*, Fig. 6). The age distribution of first contacts shows that they were largely in the reproductive age groups. This reflects concern about their risks of having affected children and about affected children born. Two thirds of the contacts at risk of having affected children were seen retrospectively, that is after the birth of an affected or at risk child. Among first contacts who were married and at risk of having affected children, almost 40% had no children (MNC) or had only affected children (MAC) so far. Genetic counselling was thus very relevant to them at this stage in their family life.

Risks and Mode of Inheritance. A tabulation by mode of inheritance of the numbers affected and the numbers at risk is given in Table I. In some 114 of the families recorded, the disease was not serious or judged to be not genetic. No further persons in these families were considered to be at risk. Among the families with chromosomal abnormalities or with multifactorial inherited conditions, there were relatively few persons at risk. By contrast, for diseases inherited in a simple Mendelian manner, a high proportion of the families had persons at risk; autosomal dominant (AD) 90%, autosomal recessive (AR) 53%, X-linked recessive (XR) 84%. This confirms theoretical calculations (Smith, 1970) that preventive methods will be most effective for the simply inherited genetic diseases.

The numbers affected reflect the burden of the genetic conditions on these families. There was an average of over three persons affected per family for the AD conditions, two persons for the XR conditions, and about 1·5 persons for the AR and multifactorial conditions. Moreover, the burden to the family is a continuing one in that a high proportion (over two thirds) of the affected persons are still alive.

The future prospects for these families are also serious because many have further members at risk either of becoming affected themselves or of having affected children. The distribution of the numbers at risk is shown in Fig. 4. Half the families with persons at risk had more than one member at risk and some families had many members at risk. In Table I, the three categories listed under 'number at risk' are mutually exclusive so their total indicates the total number at risk in these families. This averages 4·0 persons for AD conditions, 3·5 persons

TABLE I

MODE OF INHERITANCE OF NUMBERS AFFECTED AND NUMBERS AT RISK IN 559 FAMILIES ASCERTAINED

	Serious Genetic Conditions					Others*
	Mode of Inheritance					
	Autosomal Dominant	Autosomal Recessive	X-linked Recessive†	Multi-factorial	Chromo-somal	
Families						
Number	124	112	102	78	29	114
Number with someone at risk‡	111	59	86	18	2	0
Persons						
Number affected						
All	361	157	198	113	32	90
Alive	255	119	137	68	24	72
Number at risk						
Only of becoming affected	39	5	15	4	0	0
Both of becoming affected and of having affected children**	239	0	15	2	0	0
Only of having affected children**,††	158	54	272	16	2	0
Births since 1960 at risk a priori						
Number of children						
Affected	23	14	21	3	0	0
At risk††	77	2	77	3	0	0
Not at risk	8	15	12	1	0	0

* Not serious, not resolved, not genetic. † 93 Families with muscular dystrophy. ‡ Risk 10% or higher. ** Persons under age 40. †† Includes carrier daughters in X-linked disorders. (For other details see text.)

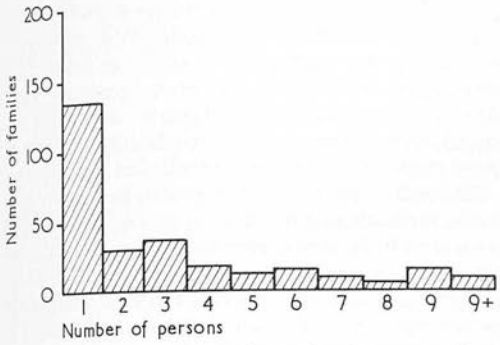

FIG. 4. Distribution of families by the number of persons at risk.

for XR conditions, and about one person for AR and multifactorial conditions.

Individuals at Risk. People at risk of becoming affected were largely in families with AD conditions with late onset (Table I), where a parent becomes affected after his children (and even grandchildren) have been born. With increasing age the risks to the children (if still unaffected), and to the grandchildren, will gradually fall. These patterns are reflected in the distribution by age of the numbers at risk of becoming affected (Fig. 5).

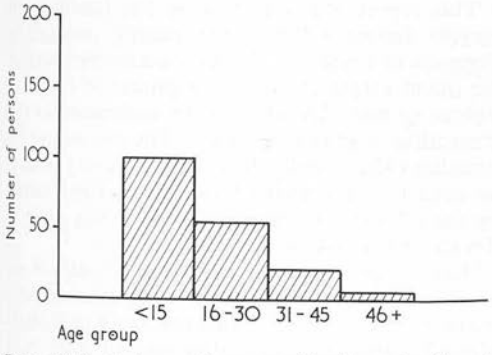

FIG. 5. Distribution by age of persons at risk of becoming affected.

For individuals at risk of having affected children or children at risk, all three simple modes of inheritance (AD, AR, and XR) were involved, although the AD-inherited conditions again predominated. The distribution of risks by age is given in Table II. The risks fall naturally into 3 groups; at about 50%, at around 25%, and from 10 to 19%. The latter group represent only 14% of all at risk, so it is the higher risk categories which predominate. The distribution of the risks also changes with age ($\chi^2 = 35$, $p < 0{\cdot}001$) with the proportion in the highest risk category increasing with age. This was largely because such high risks occur firstly, in AD conditions when the person is diagnosed as affected and onset is often late and secondly, in XR conditions when a mother is proven to be a carrier after the birth of an affected son.

TABLE II

NUMBERS, BY AGE AND RISK, OF PERSONS AT RISK OF HAVING AFFECTED CHILDREN

Age (yr)	Percentage Risk		
	10–19%	20–29%	over 30%
Under 16	29	122	41
16–30	36	94	98
31–40	19	44	60

The distribution by relationship of the proband to those at risk in the family is given in Fig. 6. There is a strong contrast with the equivalent distribution for first contacts (Fig. 3). This demonstrates that many kinds of relatives who are at high risk are not being ascertained or counselled by normal medical practice.

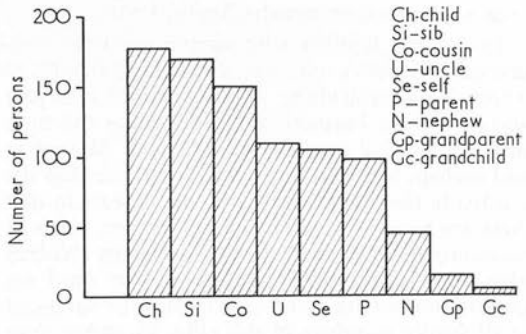

FIG. 6. Distribution of persons at risk of having affected children, by relationship of the proband.

Births at Risk *a priori*. The results for children born since 1960 to parents who where at risk *a priori* of having affected children confirm the risks involved. Of 256 births in this category, some 61 (24%) of the children were affected while a further 159 (61%), though normal so far, are still at risk of becoming affected themselves or of having affected children.

Discussion

In this department a genetic register system is being developed and is referred to by the acronym 'RAPID' (Register for the Ascertainment and Prevention of Inherited Disease). Here we report results for the initial stage of development of the register, using some 559 ascertained families. The objectives in this stage were (1) to gain experience in recording and handling family data and in assessing risks to family members and (2) to examine the need and scope for a preventive system in practice. Our results clearly show the area where preventive effort can be best applied and justify the implementation of a genetic register system in practice.

The main scope for preventing genetic disease lies, at present, with the simply inherited diseases despite the fact that other diseases are much more frequent in the population. This is because the proportion of individuals at risk is greater, and the risks are higher in families with simply inherited conditions than in families with multifactorial or chromosomal disorders. Thus it is proposed that preventive effort should be largely restricted, at least initially, to the simply inherited conditions. Thus we have defined a discrete problem area which should give worthwhile returns for any resources committed. However, it should be emphasized that even for the simply inherited disorders, it will be possible to prevent only a proportion of cases, since some will occur in families which have not been ascertained previously (Smith, 1970).

In the 338 families with simply inherited conditions, there were some 716 affected individuals, of whom 511 are still alive. This emphasizes the past and continuing burdens on these families and their need for medical care and supervision. Moreover, and perhaps more disconcerting, is the fact that the burden in these families is likely to increase in that there are some 797 individuals still at risk, either of becoming affected themselves or of having children who may be affected. This shows the need for genetic counselling and supervision to be extended to all family members at risk (Fig. 6), rather than only to the first contact in the family. That is, the initiative in prevention should be undertaken as a health service, rather than left to the individual who may be unaware of his risk. This point was stressed in a previous study (Emery and Smith, 1970) where it was shown that only a small proportion (14%) of those at risk was referred for genetic counselling. There is at present no defined procedure or responsibility for tracing and counselling individuals known to be at risk. Herein lies the value of a genetic register system.

The development of the RAPID system is now proceeding in several areas. One is to follow-up individuals who have been counselled, to keep in touch with the family, and to assess the value of the counselling methods in preventing genetic disease. Another is to develop procedures for contacting and counselling others at risk in the family, working always through the general practitioner of the person concerned. To extend the system to a population basis, methods and sources for ascertaining families with simply inherited genetic disease are being examined. Through linkage with hospital, GP, health department, and other records, relevant families will be screened for investigation and counselling. The data storage and handling operations are being organized around a computer, and much of the system software has been written. The procedures include data vetting, monitoring, listing, updating, scheduling for follow-up, and other items. Several hurdles are foreseen. Among them are the geographical dispersion of family members, security of data on file, the privacy of the individual, the attitude of healthy individuals to possible genetic risks, the effectiveness of counselling, and the organizational details required to make the register an effective preventive system.

Summary

This report concerns data on 559 families with genetic disease referred for genetic counselling, diagnosis or research. It summarizes our work on the initial stages in the development of a genetic register system (RAPID) for the ascertainment and prevention of genetic disease. The procedures for assessing risks to individuals in ascertained families are described, and methods of recording and handling the relevant family records and details on individuals 'at risk' are also shown.

Data are presented on reasons and routes of referral and on social class of the families ascertained and on the age, marital status, risk etc of individuals referred. In the 559 families studied there were 951 affected individuals (of whom 70% were still alive) and some 821 individuals who were judged to be at risk themselves or at risk of having affected children. The analyses confirm the need for a genetic register system in practice and show that the simply inherited genetic diseases offer the best scope in prevention.

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Discriminating between different modes of inheritance in genetic disease

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A genetics program library (Morton 1969a) was used to study the problem of discrimination between different modes of inheritance in genetic disease. Data were generated on familial frequencies and on the distribution of affected sibships by a two-allele single-locus model and the goodness of fit was tested by a multifactorial model to the data and *vice versa*.

The single-locus model is very flexible and can fit multifactorial data well except when the frequency is very low and the heritability is high. The multifactorial model gives a poor fit in simple Mendelian-like situations, but the fit improves as the parameters of the single-locus model become less Mendelian. In general it will be difficult to discriminate between models of inheritance with the types of data and forms of analyses studied. Even segregation analysis does not seem critical in discrimination, but rather serves to confirm the results derived from the familial frequency data. In practice, with sampling errors, ascertainment biases, mortality, variable onset age, heterogeneity, and many other complicating factors, discrimination between different modes of inheritance is likely to be very difficult indeed.

The quest for the mode of inheritance in genetic diseases has engendered much research effort and much controversy among human geneticists. Yet, despite so much interest and research, many genetic diseases are still unresolved. Why is this so, and can we hope to solve the problem in the future by developing more critical and powerful analytical tests or by collecting special sets of data?

This paper reports the results of an empirical study on the problem of discriminating between different models in genetic disease, by generating data on one model and testing the fit to this data by another model and *vice versa*. The development of a special suite of computer programs (Morton 1969a) enabling us to generate and analyse data by different models made this approach possible. A theoretical solution to this problem would appear very difficult in view of its algebraic complexity, but James (1971) has obtained some general results.

Genetic Models

One reason for the difficulty in discriminating between different modes of inheritance is that on all models the risks to relatives tend to increase with the degree of relationship to affected individuals (Edwards 1960). Thus the ranking in risks for different degrees of relationship is similar with different models. Methods of analysis therefore have to depend on the differences in risks, rather than differences in pattern, to discriminate between models.

A wide range of genetic models is possible but here the problem is restricted to two extreme models and our ability to discriminate between them. If discrimination

is difficult between the extreme models, then it is likely to be even more difficult among intermediate models.

At one extreme we consider the two-allele single-locus model recently put into a more general form by Elston & Campbell (1970) and Morton, Yee & Lew (1971), namely:

Genotype	AA	Aa	aa
Frequency	p^2	$2pq$	q^2
Proportion affected	z	$z+dt$	$z+t$

with t the level of penetrance, d the dominance, and z the proportion of non-genetic (or environmental) cases. James (1971) has shown that there are only three independent parameters in this model, namely the additive and dominance genetic variance and the population frequency of the disease. Therefore, to obtain a unique solution with the single-locus model, at least one parameter (z, d, t, or q) must be fixed.

At the other extreme we consider the multifactorial model of inheritance (Falconer 1965). This model assumes an underlying continuous scale of liability to affection, the liability being made up of many genetic and environmental factors and thus is normally distributed. The disease becomes manifest when the liability exceeds a critical threshold level. This model has only two parameters, the population frequency (P) and the heritability of liability (h^2).

Methods

The method of approach was to generate data on the single-locus model and to test the goodness of fit of the multifactorial model to this data and *vice versa*. The general plan of the analysis is shown in Table 1. Data of two kinds were generated. The first gave the *familial frequencies* (e.g. Table 3) in relatives of affected individuals. The second gave the *distribution of sibships* of s individuals with r affected (e.g. Table 5), as required for segregation analysis (Morton 1969b).

To generate the distribution of sibships

Table 1

Plan of the analysis; models, parameters, and programs used

Model and parameters	Form of data	Generated by	No. of cases studied	Goodness of fit tested by	
				Model	Program
Multifactorial	Familial frequencies in relatives	Numerical integration (Smith 1970)	9	Load Single-locus	DISQUAC UNILOC
Frequency (**P**) Heritability (**h²**)					
	Distribution of sibships		9	Single-locus	COMSEG
Single-locus Penetrance (**t**) Dominance (**d**) Non-genetic (**z**)	Familial frequencies in relatives	UNILOC	54	Multifactorial	DISQUAC
Gene frequency (**q**)	Distribution of sibships	COMSEG	0		COMSEG*

* This section of COMSEG was not available in time for this analysis.

for the single-locus model, the computer program COMSEG (Morton, et al. 1971) was used. This program (1) derives the proportion of each genotype among affected individuals, (2) generates a mating-type frequency matrix, (3) derives the distribution of sibships of s children with r affected, (4) tests the fit for an initial set of parameters to a given body of data on the distribution of sibships, (5) iterates for one to three specified parameters (t, d, z, or q) to obtain a better fit to the data, and (6) lists the final parameter set and the goodness of fit. Without iteration this program allows us to generate data on the distribution of sibships, and with iteration to seek a parameter set which provides a good fit to data generated by another model. Further development of COMSEG has made it possible to use the multifactorial model in segregation analysis, but this section of the program was not available for the present analysis.

Another computer program UNILOC, using the same single-locus model and similar computing procedures, allows us to generate the familial frequencies for relatives of affected individuals and correspondingly to seek a parameter set with a good fit to data generated by an alternative model.

A further computer program DISQUAC (Morton, Yee, Elston & Lew 1970) allows us to test the goodness of fit of the multifactorial model to familial frequency data generated by the single-locus model. Two other models can be tested by this program. One is an alternative to the threshold model. Edwards (1967) suggested a continuous *genetic* liability with an exponential risk function. However, it can be shown that the threshold model also implies a continuous genetic liability but with a cumulative normal risk function (Smith 1970). Since the latter is more reasonable and the two methods always gave similar results, the Edwards model was dropped from the analysis. The third model available for testing by DISQUAC is the load model (Morton et al. 1970). Here it is proposed that in addition to many loci with small (microphenic), mostly additive effects, there may be a few loci with large (megaphenic) effects which are partially dominant. In the absence of inbreeding, as in this analysis, the load in relatives of affected individuals can be written as $A+CR$ and the proportion affected is $(1-e^{-A-CR})$ where A is the population frequency, R the degree of relationship of the relative, and C is a measure of additive effects over all loci. Given the population frequency and the frequencies in relatives of affected individuals, we can find the value of C giving the best fit to the data.

The familial frequencies for multifactorial inheritance were taken from Smith (1970). These were derived by numerical integration of the normal curve, a method which removes biases inherent in the original threshold model. To generate the distribution of sibships with affected children, and to calculate the risks for children if 0, 1, or 2 parents are affected, the numerical integration must include separate genetic distributions for both parents. The methods are fully described by Smith (1971) in estimating recurrence risks with multifactorial inheritance. The procedure giving the frequency of sibships of size s with r affected is of the form

$$\sum_{FM}\sum Q_{FM}\binom{s}{r}(1-P_O)^{s-r}P_O{}^r \Big/ \sum_{FM}\sum Q_{FM}$$

If the father (F) is affected and the mother (M) is normal,

$$Q_{FM} = f_F f_M P_F (1-P_M)$$

where f_F and P_F are the frequency and risk to fathers of genotype class F, and similarly for mothers. P_O is then the risk to offspring of the particular parental genotype class combination (F,M). Given the frequency

(P) in the population and the heritability (h^2), expressions of this form can be quickly evaluated by computer, generating familial frequencies and distributions of sibships for any situation.

Parameter Sets

We can deal with only a limited number of cases for each model, so we must choose sets of parameters which will cover a wide range or are of special interest. For the multifactorial model the choice is easy because of the simple graphical relation between population frequency, frequency in relatives, and the heritability (Falconer 1965). Selection of three levels of population frequency (P = 0.1%, 1%, and 10%) and three levels of heritability (h^2 = 20%, 50%, and 80%) gives 9 parameter sets that span a wide range of situations possible in practice.

For the single-locus model with three independent parameters, the choice of parameter sets is more difficult. However, one restriction that can easily be applied is to arrange for the same population frequencies as chosen for the multifactorial case. Then, given values of the parameters z, d, and t, the gene frequency q corresponding to the population frequency P can be calculated. The situations of most interest are those where there are small deviations from strict Mendelian inheritance. Two series of parameter sets were chosen. In one, each of the parameters (z, d, and t) in turn was allowed to deviate from an otherwise strict Mendelian situation. The thirty parameter sets chosen in this series are shown in Table 7. In the other series, all three parameters (z, d, and t) were allowed to vary simultaneously from a Mendelian situation and here twenty-four parameter sets were chosen (Table 8).

Sample Data

The computer programs were designed for analysing numbers rather than frequencies, so it was necessary to choose numbers for each class of relative considered. The numbers used were based on a family study of diabetics (Smith, Falconer & Duncan 1971) and chosen to simulate a study with 1000 probands and some 16,000 relatives. A population of 1 million and a collection of 200 MZ twins were also used. The details are given in Table 3. The total number of relatives, or the distribution among groups, should have little effect on the general results of the analysis. This was confirmed by varying numbers in the groups and also by dropping some groups from the analysis.

For segregation analysis, 1000 sibships of size four were generated for each parental class (0, 1, or 2 parents affected) giving the equivalent of 18,000 individuals recorded. In practice most sibships would be from normal parents, with few from 1 or 2 affected parents. The choice of an equal number (1000) of sibships in each parental class will thus make our tests much more sensitive than they would be in practice where the numbers with 1 or 2 affected parents would be small.

Goodness of Fit

To obtain the maximum likelihood fit to the data, the computer programs iterate over one or more parameters. The best fit of the model to the data is then expressed as a goodness of fit χ^2. Since there is no random element in the generated data, degress of freedom and significance tests are not relevant, but the χ^2-s are used as a scale to indicate the goodness of fit obtained. A perfect fit gives a χ^2 of zero, low χ^2-s indicate good fits, while a poor fit to the data will give a large χ^2. However, the same χ^2 value may not represent equivalent levels of fit at different disease frequencies. This is because the χ^2 depends on the number of affected individuals in each class of

relative, rather than on the total number in each class. Thus the same χ^2 value will represent a better fit to the data if the frequency of the disease is high in relatives than if the frequency is low.

With the two parameter models, convergence to a solution is usually rapid. But for the single-locus model with three independent parameters, choice of the initial values for the parameters (and of the number fitted) is often critical for convergence. Thus to explore the likelihood surface, a wide range of initial parameters is tried and the most promising sets are then surveyed in more detail until no further improvement is obtained. However, there may well exist better parameter sets than those obtained by the above procedure. Moreover, it was found that several parameter sets could achieve the same goodness of fit, and so a derived set does not provide a unique solution.

Sensitivity of Analysis

Before testing the fit of one model to data generated by another model, it is important to gauge how sensitive the analyses are to departures from expectation on the original model. On the one hand, the methods must be robust enough to accommodate sampling or other biases likely in collected data. On the other, they must be sensitive enough to discriminate among different models tested.

A series of analyses were run to gauge the effects of errors in the frequency estimates on the goodness of fit χ^2s. Some results are shown in Table 2 for different kinds and amounts of error. Small errors in the frequency of one or more classes seem to have little effect on the fit achieved or on the parameters obtained. This corresponds to the situation where there are sampling errors in estimating the true frequencies. However, as the errors get larger, the fit rapidly deteriorates and high χ^2s are obtained. Thus, in practice, if some of the frequencies are in error, or if there are biases in the data, the fit to the true model may be impaired and it may be difficult to distinguish between alternative models. However, in the analysis of generated data,

Table 2

A guide to the effect of errors in frequency estimates on the goodness of fit χ^2

Source of error in frequency estimate		Goodness of fit χ^2	
		Multifactorial* (DISQUAC)	Single-locus (UNILOC)
No error in frequency estimates		<1	<1
Population frequency estimate in error by:	± 10%	<1	<1
	± 30%	7	5
	± 50%	29	135
Frequency for MZ twins overestimated by:	10%	<1	<1
	30%	2	10
	50%	9	41
Frequencies for two of the classes of relatives overestimated (or underestimated) by:	10%	3	5
	30%	20	83
	50%	71	285
Frequencies for some of the classes of relatives overestimated and other classes underestimated by:	10%	6	20
	30%	52	116
	50%	160	620

* Multifactorial: population frequency 1%, heritability 50%.
Single-locus: population frequency 2.8%, **t** = 0.9, **d** = 0.1, **z** = .0025, **q** = 0.1.

Table 3

Frequency (× 1000) of affected relatives for multifactorial inheritance and the best fits achieved by the single-locus model and by the load model

Class of relative	No. per class	Frequency (×1000)		
		Multifactorial data*	Single-locus †	Load
Population	1,000,000	1	1	1
MZ twins	200	255	114	53
Sibs	4,000	28	38	27
Parents and children	4,000	28	19	14
2nd degree	4,000	7	10	8
3rd degree	4,000	3	6	3
Goodness of fit, chi-square		<1	77	191

* Population frequency 0.1%, heritability 80%.
† **t** = 0.9, **d** = 0.03, **z** = 0.0002, **q** = 0.01.

Table 4

Best fits achieved to multifactorial data by the load model (χ^2_L) and by the single-locus model (χ^2_S) for familial frequencies, and by the single-locus model (χ^2_{SR}) in segregation analysis

Population frequency (P) (%)	Goodness of fit χ^2 and parameters			
		Heritability (%)		
		20	50	80
0.1	χ^2_L	<1	13	191
	χ^2_S	<1	8	77
	χ^2_{SR}	<1	2	6
	t	0.002	0.33	0.90
	d	1.0	0.06	0.03
	z	0.0008	0.0004	0.0002
	q	0.07	0.014	0.01
1.0	χ^2_L	<1	12	94
	χ^2_S	<1	8	68
	χ^2_{SR}	<1	4	18
	t	0.14	0.55	0.93
	d	0.23	0.12	0.09
	z	0.005	0.004	0.0007
	q	0.007	0.04	0.05
10.0	χ^2_L	<1	4	36
	χ^2_S	<1	2	31
	χ^2_{SR}	2	11	127
	t	0.28	0.89	0.96
	d	0.24	0.33	0.64
	z	0.04	0.04	0.04
	q	0.33	0.10	0.05

the χ^2-s should provide a good criterion of the level of fit achieved by alternative models.

Results

Fit to Multifactorial Familial Frequencies

Table 3 provides an example of data on familial frequencies generated by the multifactorial model and gives the best fits to the data achieved by the single-locus model and by the load model. The results for all nine combinations of frequency and heritability are given in Table 4. The load model provides a good fit to the multifactorial data at low and medium levels of heritability, but the fit declines as the heritability increases, especially if the disease is rare.

The single-locus model also gives a good fit to multifactorial data at low and medium levels of heritability (Table 4). However, usually this was achieved through a low penetrance or by a large non-genetic component (accounting for 40–80% of all cases) or by both. Such sets are unlikely to be acceptable to human geneticists (although they adequately account for the data) because they indicate that many other factors, some possibly genetic, are involved in expression of the disease. If this were so, then the multifactorial model with only two parameters would be a better method of summarizing the data and of predicting risks. A more plausible set of parameters might be chosen if a poorer fit to the data were accepted, but such a choice would be quite arbitrary.

As the heritability on the multifactorial model increases, the fit by the single-locus model deteriorates so that it may be possible to discriminate between the models. Carter (personal communication) suggests that this is the situation for many congenital malformations with high heritability, so that their mode of inheritance may be resolved. Table 3 shows the details of such a case. The χ^2 is high, with large discrepancies in the frequencies for MZ twins, sibs, and parents and children. However, the parameters derived are plausible, with a high penetrance and a low non-genetic component. Thus even in this case, with possible

Table 5

Distribution of sibships (size 4) for multifactorial inheritance* and the fit by the single-locus model

	No. of parents affected					
	0		1		2	
No. of affected sibs	Multifactorial*	Single-locus	Multifactorial	Single-locus	Multifactorial	Single-locus
0	965	969	852	842	570	579
1	33	29	129	139	307	291
2	2	2	17	17	100	104
3	0	0	2	2	21	23
4	0	0	0	2	2	3
Total families	1000	1000	1000	1000	1000	1000
Goodness of fit χ^2	0.82		0.91		1.58	

* Population frequency 1%, heritability 50%.

sampling errors or biases in the collected data, it may be difficult to unambiguously reject the single-locus model despite a rather poor fit to the data.

Fit to Multifactorial Segregation Data

An example of the fit of the single-locus model to data on the distribution of sibships with 0, 1, or 2 affected parents is given in Table 5. The results for the nine multifactorial combinations are given in Table 4. Apart from one case ($P = 10\%$, $h^2 = 80\%$), the fits obtained are all good. Moreover, they can usually be achieved with the parameter set derived in the previous section from the familial frequencies. This result was surprising but it shows that the same single-locus parameter set can mimic both the familial frequencies and the distribution of sibships found with multifactorial inheritance. Thus segregation analysis will tend to confirm the parameters found from analysis of familial frequencies rather than provide another basis for distinction between different modes of inheritance.

Fit to Single-locus Familial Frequencies

With a good Mendelian locus, penetrance is complete ($t=1$), expression is either dominant ($d=1$) or recessive ($d=0$), and all cases are due to the locus ($z=0$). What is the effect of changes in each of these parameters in obscuring a single-locus situation, so that it may be confused with another model? The combinations of parameters studied are set out in Tables 7 and 8, adjusting the gene frequency to obtain the same disease frequencies (0.1%, 1%, and 10%) as before. Table 6 shows the form of the generated data and the fit achieved by the multifactorial model.

The results when only one parameter is allowed to deviate from a strict Mendelian situation are given in Table 7. In general very poor fits to the data are achieved by the multifactorial model. In addition, the overall estimate of heritability often exceeds 100% or, if not, then one or more of estimates from particular groups of relatives may do so. Thus it seems unlikely that a single-locus situation of this kind would be confused with multifactorial inheritance. The same conclusions hold for the liod model which also shows poor fits with the single-locus data. However, if the frequency of the condition is high and the parameter deviates far from the strict Mendelian situation, discrimination on both models again becomes more difficult.

The results when more than one parameter deviates from a strict Mendelian situation are shown in Table 8. With rare dominant conditions the fit by the multifactorial model is again very poor and no

Table 6

Familial frequencies (× 1000) for single-locus data and the fit by the multifactorial model

Class of relative	No.	Single-locus* data	Multifactorial fit	Goodness of fit χ^2
Population	1,000,000	10	10	0
MZ twins	200	215	313	8.4
Sibs	4,000	91	80	5.5
Parents and children	4,000	70	80	6.1
2nd degree	4,000	40	31	7.7
3rd degree	4,000	25	18	7.8
Total χ^2				42.8

* **t** = 0.9, **d** = 0.1, **z** = 0.001, **q** = 0.04, population frequency 1%.

Table 7

Fit to single-locus data by the multifactorial model (listing the goodness of fit χ^2, the overall heritability estimate (h^2); and the number (n) of the separate heritability estimates exceeding 100%)

Single-locus model with	Parameters			Frequency (%) (P)								
				0.1			1.0			10.0		
	t	d	z	χ^2	h^2	n	χ^2	h^2	n	χ^2	h^2	n
Non-genetic cases ($z \neq 0$)												
Recessive	1	0	0.1P	896	119	3	532	108	3	165	102	1
	1	0	0.5P	508	96	1	298	78	1	84	57	0
Dominant	1	1	0.1P	2593*	184	4	919*	174	4	42	148	4
	1	1	0.5P	1698*	144	4	523*	127	4	17*	91	0
Manifesting heterozygote ($d \neq 0$)												
Recessive	1	0.01	0	439	102	3	423	107	3	179	110	1
	1	0.10	0	267*	87	3	62*	87	3	35	87	0
Incomplete penetrance ($t \neq 1$)												
Recessive	0.9	0	0	869	119	3	495	110	3	134	105	1
	0.5	0	0	–	–	3	173	86	1	17	68	0
Dominant	0.9	1	0	2599	184	4	920*	174	4	41	146	4
	0.5	1	0	1693*	145	4	516*	127	4	9*	83	0

* Better fit obtained by the load model.

ambiguity between the models should arise. However, with recessivity the fits improve as the frequency increases and as the deviation in the parameters increase. In such cases it would again be difficult to discriminate between the models in practice.

Discussion

The results of these analyses show that in many circumstances it may be very difficult to discriminate between different models of inheritance in genetic disease. The generalization of the single-locus model allows it to cover a wide range of situations, including many previously taken as evidence in support of multifactorial inheritance (e. g. Carter 1969), such as variable family risks and increased risks to relatives with severity of the proband. But this range and flexibility of the single-locus model also limits its usefulness, in that it renders the model non-diagnostic. On the other hand, where inheritance is close to the simple Mendelian form, it should be possible to reject the multifactorial model. Where there is an overlap, and discrimination is not possible, then the data may be best summarized by the multifactorial model with only two parameters.

James (1971) has given some theoretical insight into the problem of discrimination between models which complements the results presented here. On the single-locus model he has shown that the risk in relatives (P_R) can be written $P_R = P + (b_{RA} V_A + b_{RD} V_D)/P$, where V_A and V_D are the additive and dominance genetic variances and the b's are their coeffients in the ex-

Table 8

Fit to single-locus data by the multifactorial model (details as Table 7)

Single-locus model with	Parameters			Frequency (%) (P)								
	t	d	z	0.1			1.0			10.0		
				χ^2	h^2	n	χ^2	h^2	n	χ^2	h^2	n
Recessivity												
High penetrance												
Low z	0.9	0.1	0.1P	196*	80	2	43*	69	0	25	74	0
High z	0.9	0.1	0.5P	78*	64	2	8*	45	0	12	40	0
Low penetrance												
Low z	0.5	0.1	0.1P	85*	67	2	20	57	0	6	51	0
High z	0.5	0.1	0.5P	29*	52	0	3	35	0	4	28	0
Dominance												
High penetrance												
Low z	0.9	1.0	0.1P	2463*	176	4	856*	163	4	40*	137	4
High z	0.9	1.0	0.5P	1592*	141	4	463*	122	4	20*	90	0
Low penetrance												
Low z	0.5	1.0	0.1P	1528*	139	4	452*	120	4	11*	72	0
High z	0.5	1.0	0.5P	815*	113	4	188*	91	2	4	54	0

* Better fit obtained by the load model.

pressions for the covariance between relatives (e.g. Falconer 1960). James points out that the single-locus model cannot give rise to epistatic variance, while the additive multifactorial model gives no dominance variance. This difference in form of genetic variance generated is the basis for discrimination between the models. Thus, if the multifactorial model is true, it may give a better fit than the single-locus model to frequency data on relatives only if it generates appreciable epistatic variance on the observed (normal or affected) scale. It was in fact shown by Dempster & Lerner (1950) that this condition exists when the heritability of liability is high and the population frequency is low. However, as James points out, the epistatic variance components have small coefficients in the covariance between relatives and they are correlated with the coefficients for the additive and dominance variances. Thus despite the difference in the form of the variance generated, it may only be in extreme situations that discrimination between the two models is possible. This is confirmed in the present analysis in that the fit by the single-locus model to multifactorial data decreases as the heritability rises and as the frequency falls, until at some level discrimination may be possible.

If data on consanguinity are available, the analytical methods used may be more powerful in discriminating between different models (Morton 1967, Morton et al. 1970). For additive effects the mean should be unchanged by inbreeding (F), while the additive genetic variance increases by a factor $(1+F)$. However, this pattern may not hold for liability and disease frequency. As loci not normally associated with liability become homozygous, the biochemical and physiological status of the individual may change, and with this background change, the mean liability and the risks of affection may also be changed. For example, differences in frequency of a disease between sexes reflect the effects of a changed physiological and hormonal status on the mean liability, and consanguinity may have similar effects. Thus with traits such as disease, a raised frequency on con-

sanguinity may not be diagnostic of rare recessive inheritance but may be due to other factors.

Other recent approaches to discriminate between different modes of inheritance might be of interest. Reich (1971) has suggested that where a disease has two (or more) threshold levels, the relative familial frequencies for the two thresholds may differ for the single-locus and multifactorial models, so that it may be possible to discriminate between them. Slater (1966) has shown how the distribution of affected relatives on the paternal versus the maternal side of the pedigree may help to distinguish between multifactorial inheritance and a dominant major gene with diminished penetrance. More recently. Elston (personal communication) suggests that multigeneration segregation analysis may be useful in discriminating between different modes of inheritance.

Although the extreme modes of inheritance have been considered here, a whole spectrum of other models is possible. For example, diseases may be associated with multiple alleles at one locus, or involve the joint action of two or more loci. Alternatively a condition may be heterogeneous, either clinically or biochemically, and clearly the resolution of the heterogeneity would then be important.

The problems of discrimination become even more difficult in practice. There will be sampling errors in the data collected and there may be biases in ascertainment, diagnosis, and classification. Non-genetic familial effects will have to be discounted and modifications made for sex differences in frequency, variable onset age, severity, and differential mortality. Proof of the exact mode of inheritance may be possible only if a fairly strict Mendelian pattern is discernible, or if biochemical variants associated with the disease can be demonstrated (Fredrickson 1969). Usually the results of analyses, such as these described here, will not be unambiguous and so the controversy about the mode of inheritance in genetic diseases is likely to continue.

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A statistical and genetical study of diabetes

II. Heritability of liability

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INTRODUCTION

In the past several different models of inheritance have been fitted to familial data on diabetes, and a plausible fit by the model proposed has usually been obtained (e.g. Harris, 1950; Steinberg, 1959; Post, 1962; Barrai & Cann, 1965; Falconer, 1967; Simpson, 1969). In practice it may be difficult to distinguish between different modes of inheritance, unless a fairly strict Mendelian pattern obtains (Smith, 1971). This is because different models may give similar familial frequencies and similar distributions of segregation patterns among families. In this paper, the main method used in analysis is the heritability of liability model (Crittenden, 1961; Falconer, 1965). Simpson (1964) proposed a multifactorial mode of inheritance for diabetes and the liability model has been used successfully in the analysis and interpretation of familial data (Falconer, 1967; Simpson, 1969). This paper presents further independent estimates of heritability of liability to diabetes and examines several new aspects. These are (1) the effects of common environmental factors on familial frequencies (from data on the spouses of patients and on spouses of relatives), (2) the genetic correlation between 'early-onset' and 'late-onset' diabetes (from data on age of diagnosis in patients and in their affected relatives), (3) estimates of heritability from second- and third-degree relatives, and (4) an appraisal of factors, such as mortality, which may bias the estimates of heritability (this is presented in the Appendix). The variable onset-age and the logarithmic increase in prevalence with age introduce several complications in the genetic analysis, and so the methods used are described in some detail. Estimation of the population prevalence was described in the first paper of this series (Falconer, Duncan & Smith 1971), where the factors affecting morbidity were examined.

SOURCES OF DATA

For a heritability analysis, estimates are required of (1) the frequency of diabetes in the population and of (2) the frequency of diabetes among the relatives of diabetics. The frequency of diabetes in Edinburgh was estimated by ascertainment that was 90–95 % complete, and using the criteria (1) that the diagnosis of diabetes was confirmed by a doctor and (2) that the diabetic was alive and living in Edinburgh on a given date. Details of the procedure and results were presented in the first paper of this series (Falconer *et al.* 1971). The results pertinent to the present paper are summarized here with the age-specific prevalence by decade given in Table 1 and the frequency of diabetes in four onset-age groups given in Table 2.

Interview questionnaire

The frequency of diabetes in the relatives of diabetics was estimated through an interview questionnaire of out-patients attending the Diabetic Department at the Royal Infirmary

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Edinburgh. Some 1367 diabetics on a routine visit were questioned about the diabetic status of their relatives. Most of the interviewing was done by one person (Miss J. Henry, B.Sc.) over a period of one year. Full details were taken on each patient and these were checked later with the clinic files. Information on relatives was sought in a routine order so as to cover the whole family systematically and to elicit recall of the second- and third-degree relatives by tracing each branch of the family through a first-degree relative. The order was spouse, father, father's sibs (paternal uncles and aunts) in order with their children (paternal cousins), and similarly for the maternal

Table 1. *Age-specific prevalence of diabetes in Edinburgh*

Current age (years)	Age-specific prevalence (%)		
	Males	Females	All
0– 9	0·010	0·016	0·013
10–19	0·092	0·094	0·093
20–29	0·209	0·195	0·202
30–39	0·306	0·259	0·282
40–49	0·641	0·434	0·531
50–59	0·995	0·817	0·898
60–69	1·750	1·880	1·830
70–79	2·090	2·300	2·230
80–89	1·530	1·530	1·530

Table 2. *Numbers and percentage affected in onset-age groups*

Onset-age group (years)	Population (000's)	No. affected	% affected
0–24	468·0	304	0·064
25–44	290·4	529	0·182
45–64	180·3	1458	0·808
65–84	61·9	658	1·063
25–84	290·4	2645	0·912

side; then sibs in order with their spouses and their children (nephews and nieces to the patient); and finally the patient's children in order with their spouses and their children (grandchildren to the patient). The total number reported for each class of relative is given in Table 3. For each relative the detailed relationship to the patient was recorded, along with the name, sex, current age (or age and year at death), address (where available) and diabetic status. If the relative was diabetic then the age at onset and current treatment (diet alone, oral hypoglycaemic or insulin) were also recorded. Sixty-one per cent of the patients had no affected relatives, 26 % had one, 9 % had two, and 4 % had more than two affected relatives. In all, 821 relatives, or 3·1 % were affected compared with the population prevalence of 0·63 %.

Reliability of interview data

Several checks were made on the reliability of the data given by the patients at interview. The patients' own details were checked with the clinic-file records and were found to be quite accurate. For 100 of the patients, relatives with an Edinburgh address were contacted asking them to confirm or correct the information given about them by the patients at interview. Useful replies were received from 563 relatives, over 70 % of those circulated. No errors were found in diabetic status and, for the 11 diabetics recorded, age at onset was accurate. The current ages of relatives

quoted by the patients, were also quite reliable, as shown by the figures in Table 4. Viewed against the wide ranges of age involved, the bias in age quoted was trivial, and the standard deviation of the errors in age was also small.

Table 3. *Numbers of relatives recorded and numbers affected with diabetes*

	No. recorded	No. affected
Parents	2,676	207
Sibs	3,892	321
Children	2,042	18
Uncles, aunts	1,690	91
Nephews, nieces	4,658	22
Grandchildren	2,275	3
Cousins	3,643	83
Patients' spouses	1,013	15
Sibs' spouses	1,896	18
Children's spouses	1,104	1
Others	746	42
Total	25,635	821

Table 4. *Summary of data on age of relatives*

Class of relative	No.	% with correct age	% with correct age ± 2 years	Standard deviation of the errors (years)
First degree	128	82	96	1·1
Second degree	217	68	83	2·6
Third degree	140	65	87	2·1
Spouse of first-degree relative	78	78	91	1·8

The diabetic status of a further 50 relatives who were said to be affected was checked. One error was detected in this sample. The relative concerned had visisted the clinic with diabetic symptoms, but test results were doubtful and he had not been classified as diabetic. The ages at onset were again found to be quite reliable, the standard deviation of errors being 1·7 years. The information given on the relative's mode of treatment also proved quite sound. Of 25 said to be using insulin, all were doing so, though two said to be on diet had an oral hypoglycaemic treatment.

Address class and frequency

If a patient could cite the complete address of a relative, it would indicate that they were in close contact, and might be likely to know more about each other's health status than if the address were unknown or partially known. To test this supposition, relatives were grouped into three classes: with (1) complete postal address, (2) address sufficient for contact, and (3) address unknown or insufficient. The percentages of affected relatives in these classes were compared, adjusting to the average age of the first class by the regression of liability on age in the population, which was +0·2 liability units per decade. The results, in Table 5, show some significant differences between classes. However, there was no consistent pattern among the different kinds of relatives and so the address classes were combined for all the subsequent analyses. Since the population frequencies refer to living diabetics, only data on living relatives were used in the heritability analysis.

Table 5. *Percentage of relatives affected (with standard error) by address class (the age distribution of the relatives has been taken into account)*

	Address complete (%)	Address sufficient (%)	Address unknown (%)
Sibs	9·8 ± 1·0	5·3 ± 0·5	4·7 ± 0·9
Parents	5·1 ± 1·0	7·3 ± 1·7	—*
Children	0·7 ± 0·3	0·7 ± 0·3	0·6 ± 0·5
Uncles, aunts	2·8 ± 1·2	4·0 ± 0·7	1·8 ± 0·6
Nephews, nieces	0·4 ± 0·2	0·4 ± 0·1	0·2 ± 0·1
Grandchildren	0·2 ± 0·1	0·0 ± 0·1	0·3 ± 0·3
Cousins	3·6 ± 0·9	2·0 ± 0·3	3·6 ± 0·5
Patients' spouses	1·6 ± 0·4	—	—
Sibs' spouses	1·3 ± 0·4	0·5 ± 0·2	1·9 ± 0·7

* Less than 100 relatives.

Selection of patients

Patients attending the clinic may be more severely affected than those not attending. This source of bias was assessed by comparing the distribution of treatment by age for patients interviewed and for all diabetics in Edinburgh. Compared with the whole population of diabetics, there were, within each group, about 5–10 % more patients on insulin, and over the age of 50 there were 8–12 % more patients on oral hypoglycaemic treatment. There were corresponding deficits of patients on diet treatment. Thus, if insulin treatment reflects severity, the average liability of patients interviewed may be higher than estimated from the population. This would lead to a slight overestimate of the heritability. An effort was made to obtain data from as many patients as possible with early onset since the number in this class was small. For this reason the average age at onset for patients interviewed (45 years) was lower than that for all confirmed diabetics (52 years).

MODELS AND METHODS

Edwards (1969) and Smith (1970) presented an unbiased version of the heritability or liability model (Falconer, 1965). However, this version is more difficult to use in complex situations, such as those involving different onset-age groups or relatives of different ages. So the simpler original model was used in the analysis and the bias in the genetic parameters later discounted.

The phenotypic correlation (t) in respect of liability between relatives of any specified sort is given by

$$t = \frac{x_g - x_r}{a_g}, \tag{1}$$

where x_g and x_r are the mean liabilities of the population and of the relatives of patients respectively, and a_g is the average deviation in liability of patients (probands) from the population mean. If environmental causes of familial resemblance are absent, the heritability of liability (h^2) in the population is given by

$$h^2 = t/R,$$

where R is Wright's coefficient of correlation between patients and relatives.

If the population can be divided into two groups (1 and 2) on the basis of sex, age, or other criterion, then a more general formula relating patients in group 1 with relatives in group 2 is

$$h_1 h_2 r_{G.12} = \frac{1}{R} \frac{x_{g2} - x_{r2}}{a_{g1}},$$

where h_1^2 and h_2^2 are the heritabilities of liability within each group, $r_{G.12}$ is the genetic correlation between the groups, and the x and a terms refer to the groups indicated (Falconer, 1967). Thus where different age-groupings are involved, the distributions of onset age and of current age must be taken into account, both for the patients and for their relatives.

Onset-age

Diabetes is a heterogeneous disorder of impaired carbohydrate tolerance and utilization. Perhaps the most important and most common clinical distinction is between severe (insulin-dependent) cases with early onset and mild (generally insulin-independent) cases with late onset. The question then arises whether these are due to distinct genetic entities or merely represent degrees of severity – in terms of metabolic derangement or insulin dependence – of the same genetic condition. The heritability model can be used to test the fit of these alternative models to observed data.

If early-onset and late-onset diabetes are manifestations of the same genetic condition, the difference of onset age reflects different phenotypic levels of liability to the same causative factors, and the genetic correlation (r_G) between the two forms of the disease will be unity. The population will form a single continuous distribution of liability, on which there are two thresholds. The more extreme threshold separates the early-onset cases with high liability, and the less extreme separates the late-onset cases with lower liability. The late-onset cases all fall between the two thresholds. This model, which is illustrated in Fig. 1 (*a*), will be called the *cumulative* model and represents the situation when $r_G = 1$. The mean liability of early-onset patients is obtained from the population frequency of early-onset cases and that of late-onset patients from the positions of the two thresholds on the distribution. It therefore depends on the frequencies both of early-onset cases (determining the upper threshold) and of late-onset together with early-onset cases (determining the lower threshold).

If early- and late-onset diabetes are due to totally different genetic factors, then there are two quite separate distributions of liability. This will be called the *separate* model representing the situation when $r_G = 0$. It is illustrated in Fig. 1 (*b*). In this case the mean liabilities of patients in each onset-age group are derived from the separate frequencies of the groups in the population.

A third, and more likely, possibility is that early- and late-onset diabetes are due partly but not entirely to the same genetic factors. The genetic correlation would then lie between 0 and 1. This will be called the *related* model: it is illustrated in Fig. 1 (*c*). If the related model represents the real situation, there is unfortunately no simple way of estimating the genetic correlation because it is not possible to obtain the mean liability of the late-onset patients. The mean liability of late-onset patients will depend both on the frequency of early-onset cases and on the phenotypic correlation between early and late onset. However, the phenotypic correlation cannot be estimated because individuals cannot be in both groups. Some form of iterative solution, involving frequencies in relatives of early- and late-onset groups may be possible but would have to take account of the underlying genetic and residual correlations as well as the phenotypic correlation.

The fit of the alternative cumulative and separate models to the observed data can be tested, estimating for each model the heritability (h^2) within each onset-group and the quantity ($h_{12} = h_1 h_2 r_{G.12}$) between onset-groups. The genetic correlation ($r_{G.12}$) on each model can then be estimated and tested against a null hypothesis of unity for the cumulative model and of zero for the separate model. The form of the analyses follows equation (2), adjusting the parameters

to the appropriate model and onset-group. For example, the mean liability in the late-onset group (Fig. 1) for the separate model is a'_2, corresponding to the frequency q_2, and for the cumulative model it is a_2, which must be derived as $a_2 = ((q_2+q_1)\,a_{(2+1)} - q_1 a_1)/q_2$. Similarly the terms in the

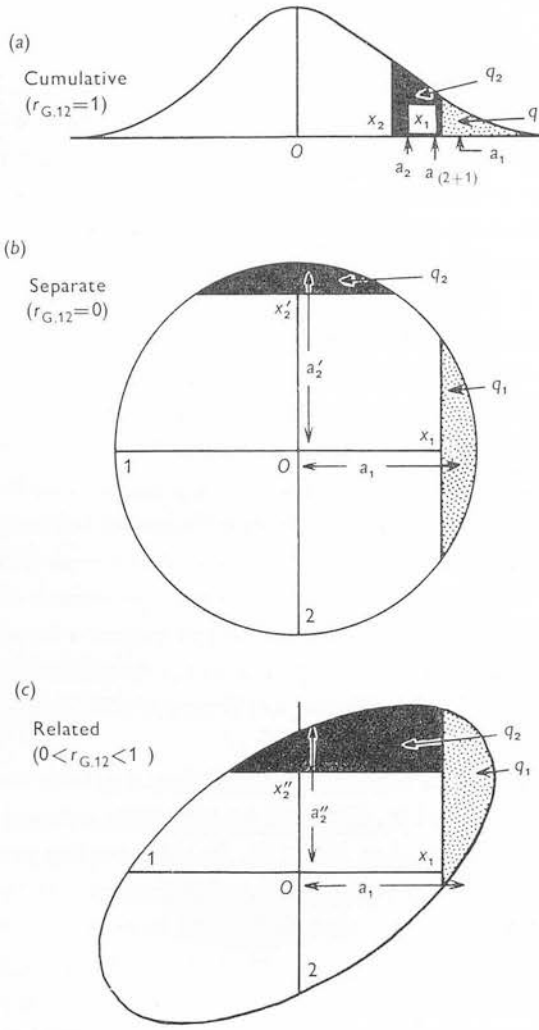

Fig. 1. Diagram to represent different genetic models for a disease with two consecutive groups identifiable (details see text); assuming (*a*) one continuous distribution of liability (the cumulative model), (*b*) two independent distributions of liability (the separate model) and (*c*) correlated distributions of liability (the related model).

numerator of equation (2) need to be derived separately for each model and onset group. The variance of the genetic correlation ($r_{G.12}$) can be estimated as

$$r^2_{G.12}\left\{\frac{4V(h_{12})}{h_{12}} + \frac{V(h_1^2)}{h_1^2} + \frac{V(h_2^2)}{h_2^2}\right\},$$

using the formulae in Falconer (1965) to estimate the variances (V) of the individual terms. In the cumulative model the terms will not be independent, and then the variance estimated will be a maximum value.

The simple dichotomy into early- and late-onset groups gives a wide range of onset-ages in the late-onset group and a great disparity in frequency between the groups. It is possible to increase the sensitivity of the analysis for the cumulative model, by dividing the onset data into several onset groups and estimating the genetic correlation in liability between groups.

Current age

The simplest estimates of the heritability of liability are derived from current age-groups (cohorts) of patients and their relatives. These estimates assume that the cumulative model holds. They are used here for comparing estimates from the two sexes, from different kinds of relatives and from different publications. As mentioned above, it is important to match the population parameters with the age distribution of the relatives being studied.

RESULTS

Non-genetic familial effects

Before undertaking a genetic analysis, it is important to establish if non-genetic familial effects are important, and if so to adjust for them. Data on spouses of patients and on spouses of first degree relatives give some information on this topic since spouses share the same environment (after marriage) but none of the heredity of their mates. Thus estimates of the correlation in liability between spouses will give a measure of the bias in the heritability estimates from relatives due to non-genetic familial effects. The estimates of the correlation between spouses, given at the bottom of Table 8, are either low or negative, with a pooled value of $-0{\cdot}01 \pm 0{\cdot}03$. This indicates that non-genetic familial effects, at least those acting after marriage, are not important in affecting the frequency of diabetes among relatives of diabetics.

Onset-age groups

In the analyses by onset-age, the separate and cumulative models can be dealt with concurrently. Two sets of analyses were made: (1) with two onset groups – under 25 years and over 25 years, and (2) with four onset groups – under 25 years, 25–44 years, 45–64 years and 65–84 years, corresponding to different phases of onset-age frequency. The frequencies of affected individuals in various onset-age groups are given in Table 2. The data on all living first-degree relatives of both sexes were pooled for the analyses and are given with the results in Tables 6 and 7. The mean age is the average age of relatives in the age-group with the age-group boundary as the upper limit. The justification for pooling data on the sexes is given later.

In the analyses for the two onset-age groups (Table 6), the estimates of heritability of liability were similar for the two onset-ages and also for the two models. The reason that two such different models give similar results is that the frequency of diabetes increases logarithmically with age so that the frequency in the first onset group has little effect on the frequency in subsequent groups, or on the heritability estimates derived from them. Turning to the estimates of genetic correlation between the onset groups, the estimates are again similar for the two models but markedly different for the two alternative onset-age combinations. This difference is examined in more detail below. However, on the basis of a pooled genetic correlation of $0{\cdot}68 \pm 0{\cdot}04$ between onset groups, the separate model would appear to be untenable and can be rejected.

The further partition of the data into four onset-age groups is made in Table 7, and analysis by the cumulative model confirms the pattern of results with two onset-age groups. Where the

patient's onset group is lower than that of his relatives, the estimates of genetic correlation are all high (pooled value $1{\cdot}00 \pm 0{\cdot}02$); but in the reverse situation the estimates are much lower (pooled value $0{\cdot}49 \pm 0{\cdot}04$) and more variable. The difference is striking and real, but is more likely to be due to non-genetic than to genetic effects. It could be well explained by the trends found

Table 6. *Number of first-degree relatives, their mean age (see text) and the number affected by onset-age group of the patient. Below: parameter estimates (with standard errors) derived for the separate and cumulative models (diagonals – heritability; off diagonals (bold type) – genetic correlations)*

		First-degree relatives: onset-age group					
		Early (under 25)			Late (over 25)		
Patient onset-age group	Model	No. affected	Total no.	Mean age	No. affected	Total no.	Mean age
Early	—	22	1075	22	36	766	49
Late	—	11	6326	25	303	5777	57
		Parameter estimates					
		Early			Late		
Early	Separate	$0{\cdot}66 \pm 0{\cdot}05$			**$0{\cdot}91 \pm 0{\cdot}05$**		
	Cumulative	$0{\cdot}65 \pm 0{\cdot}05$			**$1{\cdot}04 \pm 0{\cdot}05$**		
Late	Separate	**$0{\cdot}25 \pm 0{\cdot}07$**			$0{\cdot}66 \pm 0{\cdot}02$		
	Cumulative	**$0{\cdot}24 \pm 0{\cdot}07$**			$0{\cdot}60 \pm 0{\cdot}02$		

Table 7. *Number of first degree relatives, their mean age (see text) and the number affected by onset-age group of the patient. Below: parameter estimates (with standard errors) derived for the cumulative model (diagonals – heritability; off-diagonals (bold type) – genetic correlations)*

	First-degree relatives: onset-age group											
	< 25			25–44			45–64			65–84		
Patient onset-age group	No. affected	Total no.	Mean age	No. affected	Total no.	Mean age	No. affected	Total no.	Mean age	No. affected	Total no.	Mean age
<25	22	1075	22	20	766	41	12	455	56	4	107	74
25–44	7	1668	23	20	1344	42	41	948	59	14	414	74
45–64	3	3588	25	17	3367	43	114	2510	60	50	1165	74
65–84	1	1070	25	7	1066	44	20	815	60	20	444	76
	Parameter estimates											
	<25			25–44			45–64			65–84		
<25	$0{\cdot}65 \pm 0{\cdot}05$			**$1{\cdot}16 \pm 0{\cdot}06$**			**$0{\cdot}94 \pm 0{\cdot}05$**			**$0{\cdot}76 \pm 0{\cdot}06$**		
25–44	**$0{\cdot}64 \pm 0{\cdot}09$**			$0{\cdot}48 \pm 0{\cdot}06$			**$1{\cdot}09 \pm 0{\cdot}06$**			**$0{\cdot}94 \pm 0{\cdot}06$**		
45–64	**$-0{\cdot}03 \pm 0{\cdot}13$**			**$0{\cdot}38 \pm 0{\cdot}06$**			$0{\cdot}59 \pm 0{\cdot}03$			**$0{\cdot}98 \pm 0{\cdot}05$**		
65–84	**$-0{\cdot}03 \pm 0{\cdot}24$**			**$0{\cdot}55 \pm 0{\cdot}10$**			**$0{\cdot}83 \pm 0{\cdot}08$**			$0{\cdot}57 \pm 0{\cdot}07$		

in the previous paper of this series (Falconer *et al.* 1971). These showed that the frequency of diabetes in any onset-age group declined with earlier date of diagnosis (or increasing duration of the disease), this reduction in frequency being due either to lower detection rates in the past, or

to a higher differential mortality of diabetics. The consequence of this trend is that the frequency of early-onset cases is reduced in the higher current-age groups, and there is a high positive correlation between onset age and current age among living diabetics. There is also a positive correlation between the current ages of patients and their relatives. These correlations will affect the estimates of the genetic correlation in the following way. Patients in a late-onset group will have higher current ages, and so will their relatives. Therefore there will be a reduced frequency of living early-onset cases among the relatives of late-onset patients, and this will reduce the estimate of the genetic correlation derived from these groups. On the other hand, there will be no comparable bias in the reverse situation, early-onset patients with late-onset relatives. The reduced frequency of early-onset cases here applies to the patients and results simply in a reduced number ascertained; the frequency of late-onset cases among their relatives will not be affected. For these reasons, therefore, the genetic correlation is more reliably estimated from early-onset patients and late-onset relatives, and the estimate of about 1·0 can be accepted as the more valid.

The conclusion drawn from these analyses, then, is that early- and late-onset diabetes have the same, or a quite similar genetic causation. In other words, they derive from the same distribution of liability to the disease, or have a highly correlated bivariate distribution. The rest of the paper proceeds on the basis of a single distribution in liability. The heritability estimates for different onset-age groups, given in Table 7, show a higher value for early-onset than for medium- or late-onset cases. However, a continuing decline in heritability with increasing onset age, found by Falconer (1967) and Simpson (1969), was not apparent in these data.

Current age-groups

Patients in a current age-group (or cohort) form a composite of several onset age-groups. Heritability estimates derived from them are also composite and may be difficult to interpret. However, the estimates are easy to derive and are useful for comparisons between the sexes and between populations, and also for testing the consistency of estimates derived from different kinds of relatives.

For a direct comparison with Simpson's (1969) results, the analyses for sibs were made for the four sex combinations of patients and relatives, MM, MF, FM and FF, for each decade of age. The four sets of estimates (equation (2)) are plotted over age-groups in Fig. 2, with Simpson's results for comparison. The Edinburgh values are more variable than Simpson's since there were less data available. However, the pattern of the pooled data is consistent in showing that the estimates of heritability are higher in the Edinburgh data, and that the estimates are higher for early ages than for later ages in both sets of data.

The genetic correlations ($r_{G.FM}$) between sexes at each decade were estimated from the values in Fig. 2, and pooled over ages. The estimates from the Edinburgh data were $0{\cdot}97 \pm 0{\cdot}09$ and $1{\cdot}03 \pm 0{\cdot}09$ for the MF and FM classes respectively giving an overall estimate of $1{\cdot}00 \pm 0{\cdot}06$. With Simpson's data the estimate of the genetic correlation between sexes was $1{\cdot}03 \pm 0{\cdot}03$ for the MF class, but for the FM class the correlation was only $0{\cdot}61 \pm 0{\cdot}03$, due to a deficiency of affected brothers of female patients. Simpson was unable to explain this anomaly for the FM class, and since it was not found in the Edinburgh data we conclude that the result was probably a spurious one.

The change in heritability with age may be due to a change in the environmental variance or to a change in the mean liability, or to both. Falconer (1967) (equations (3) and (5)) showed how

it may be possible to differentiate between these possibilities. As a means of detecting a change of mean liability, he suggested expressing the liability in genetic, instead of phenotypic, standard deviation units, since the genetic variance is more likely to be constant than the phenotypic variance. The mean liability at age i in genetic standard deviation units is given by x_i/h_i, where x_i is the mean liability in phenotypic units, and h_i is the square root of the heritability at age i. The mean liability, expressed as x_i/h_i, showed a significant increase with increasing age in the Edinburgh data. This supports the conclusion, based on the Canadian data, that a change in environmental variance is not sufficient to account for the reduction in heritability with age, and consequently that there must also be an increase in mean liability with increasing age.

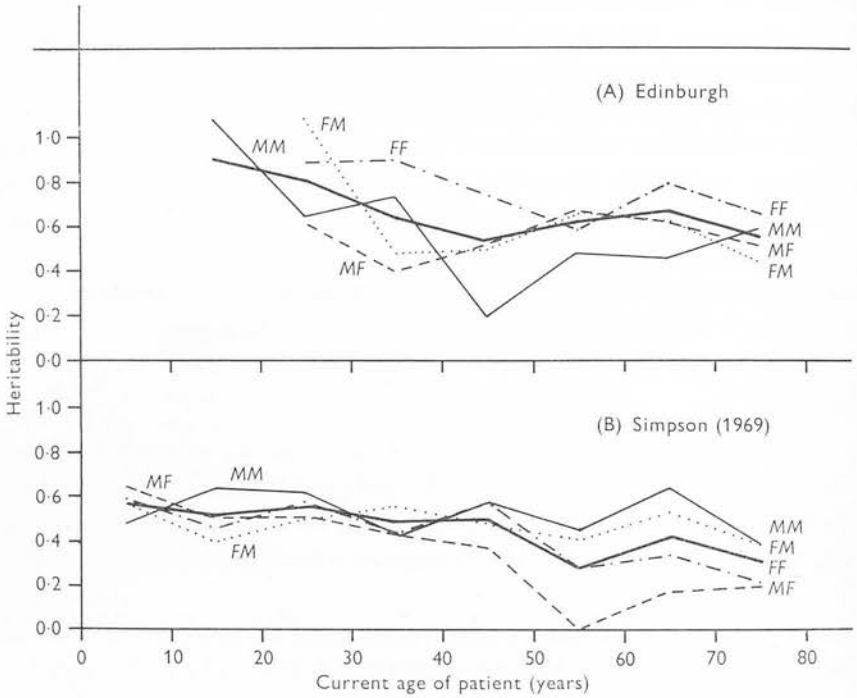

Fig. 2. Heritability estimates from sibs by current age group of patient from the present data and from Simpson (1969).

The overall estimates of heritability derived from different kinds of relatives are given in Table 8. These estimates take into account the age distribution of patients and of relatives as described by Falconer (1967). The low estimates of correlation in liability between spouses have already been noted and indicate that common environmental effects, after marriage, are not important in affecting the frequency of diabetes in spouses. Since relatives tend to live apart after marriage their environmental similarities are likely to be even less than for spouses. There remains the possibility of resemblance due to similar childhood environment but there were insufficient data on adopted children to test this effect.

Estimates of heritability from different kinds of relatives were sought for several reasons: (1) to get further estimates of the parameter, (2) to test the applicability of the threshold model across all kinds of relatives, and (3) to derive estimates less influenced by any environmental effects common to first-degree relatives. The estimates of heritability obtained from different groups of

relatives were quite variable and so are difficult to interpret or account for. There was a good agreement between the estimates from sibs and parents, which were the groups with the largest numbers of affected relatives. Estimates from the other groups had much larger standard errors, but still many of the differences among groups were significant ($P < 0{\cdot}05$). The estimates from children and from the three groups of second-degree relatives were all in the 20–40 % range and were significantly lower ($P < 0{\cdot}05$) than the estimates from sibs and parents. On the other hand, the estimate of heritability from cousins was significantly higher than for others.

Table 8. *Estimates of heritability from first-, second- and third-degree relatives, and of the correlation in liability between spouses (the age distributions of the patients and of their relatives have been taken into account)*

Relative	Heritability (or correlation*)	Standard error
First degree		
Sibs	0·56	0·03
Parents (alive)	0·43	0·06
Parents (all)	0·52	0·02
Children	0·19	0·07
Second degree		
Uncles, aunts	0·38	0·09
Nephews, nieces	0·22	0·10
Grandchildren	0·24	0·25
Third degree		
Cousins	1·02	0·14
Spouses		
Patients' spouses	0·03*	0·04
Sibs' spouses	−0·02*	0·04
Children's spouses	−0·35*	0·21

The range of heritability estimates from the different kinds of relatives raises doubts about both the data collected and about the methods of analysis used. Perhaps the threshold model is not appropriate for the inheritance and expression of diabetes. But yet equally there seems to be no other genetic model that can account for the data found, namely a lower frequency in children than in parents together with a higher frequency in cousins than in second-degree relatives. A second possibility is that the environmental components among relatives may affect the various heritability estimates differently. However, it was shown that the correlation in liability between spouses was low, and this indicates that environmental effects after childhood are not important in biasing the heritability estimates. There remains the possibility of environmental effects during childhood, before marriage. If the environmental resemblance between relatives decreased less than genetic resemblance, then higher heritability estimates would be obtained from second- and third-degree relatives than from first-degree relatives. But the results for first-degree relatives were intermediate to the heritabilities estimates for the two groups so weakening the argument for common childhood environmental effects. However, cousins tend to be contemporary with the patient, while second-degree relatives are not, and this contemporaneity may increase the environmental resemblance between cousins, leading to a higher heritability estimate. Still another possibility to explain the range of heritability estimates in Table 8 is a bias in reporting. Relatives with the lowest heritability estimates (children, nephews, nieces and grandchildren) all came towards the end of the questionnaire. At this stage, the patient after an early enthusiasm

in reporting details on the first relatives cited, may have felt tired and impatient to end the interview. For these groups there may have been an under-reporting of affected cases, compared with an over-reporting for the earlier groups in the questionnaire. Because of the anomalously high heritability estimate for cousins, this group was studied in more detail. To see if the anomaly was associated with one type of cousin, the data were separated into four classes by the sexes of the parent of the patient and of his sib, the parent of the cousin. However, the frequencies of diabetic cousins were similar in the four classes, so the anomalously high heritability was common to all four classes. This would discount the role of cytoplasmic inheritance or excess recording on the maternal side in causing the high heritability estimate in cousins. Another possibility, suggested by Dr T. Reich, is an under-reporting of unaffected cousins, for this might not apply to first- and second-degree relatives, who would be easier to recall at interview. However, the average sibship sizes of cousin families of nephew–niece families were similar so there is no evidence to support Dr Reich's suggestion.

On the whole, none of the above possibilities provides a reasonable explanation for the range of heritability estimates found. Thus until this dilemma can be resolved with new data or a different model, both the current data and the threshold model must remain under some doubt in describing the inheritance of diabetes and its frequency in relatives of affected individuals.

Liability and severity

Clinically severe diabetes usually requires insulin treatment while in less severe cases an oral hypoglycaemic agent or a diet regime may be sufficient to control the disease. Is clinical severity, as indicated by the treatment required, related to genetic liability? To study this question, patients were grouped by current treatment and by onset age, and the frequency in sibs of each group was evaluated. The mean liability of sibs in each group was then expressed as a deviation from the age-matched population liability and pooled over onset groups, weighting by the inverse of the variance of the estimates. The results, given in Table 9, show a significantly lower liability of sibs of those on diet treatment, but little difference in liability between the oral hypoglycaemic and insulin groups. Thus the level of liability of the least severely affected group of patients is clearly lower than that of the two more severely affected groups. The differences of liability may

Table 9. *Treatment group of patient and liability of sibs expressed as a deviation from the age-matched population liability* (*see text*)

Treatment group of patient	Deviation in liability of sibs	Standard error
Diet	0·68	0·10
Oral hypoglycaemic	0·91	0·06
Insulin	0·95	0·06

in reality be larger than they appear because the comparisons made tend to underestimate the differences for the following reason. Treatment is likely to change from diet to oral hypoglycaemic to insulin with increasing duration of the disease. Classification by current treatment will therefore be partly a classification by duration, which is not a measure of severity. Thus it is probably justifiable to conclude that the genetic level of liability is correlated with clinical severity over the whole range of severity.

Liability and date of diagnosis

Relatives of patients with different dates of diagnosis may provide information as to whether differential mortality or changes in the detection rate is responsible for the reduced frequency of diabetics with increasing duration and earlier date of diagnosis, which was described in the earlier paper (Falconer *et al.* 1971). Both mortality and detection are likely to be connected with severity and therefore also with liability. If the reduction in frequency is due to mortality then living diabetics who were diagnosed at an early date will have a lower mean liability than those diagnosed at a later date. On the other hand, if the reduction in frequency is due to increasing detection rate, the reverse will hold and earlier diagnosis will be associated with higher mean liability.

Table 10. *Decade of diagnosis of the patient and the liability of his sibs expressed as a deviation from the age-matched population liability (see text)*

Decade of diagnosis of patient	Deviation in liability of sibs	Standard error
1960–9	0·84	0·04
1950–9	0·83	0·06
1940–9	0·71	0·13
1930–9	0·97	0·18

If both causes were operating the contrary effects might counterbalance, leaving no differences in liability associated with the date of diagnosis. The genetic level of liability of patients with different dates of diagnosis was estimated from the mean liability of their first-degree relatives. Patients were grouped by the decade of diagnosis and also by onset age. The frequency in all first-degree relatives was calculated and again the mean liability of each group expressed as a deviation from the liability of an age-matched control and pooled across onset ages. The results, given in Table 10, show no significant differences in liability of relatives of patients diagnosed in different decades. This suggests that both differential mortality and an increasing detection rate were operative. The test, however, is not very sensitive because only a fraction ($\frac{1}{2}h^2$) of the phenotypic differences between patients appears in the differences between their relatives. Thus large numbers of relatives would be required to demonstrate significant differences between groups.

DISCUSSION

In this paper we restrict our analysis and discussion to the heritability of liability model (Falconer, 1965). Later we hope to consider other forms of analysis and other modes of inheritance and also to present both empirical and theoretical risks of diabetes for individuals in diabetic families.

Though there is considerable literature on the frequency of diabetes in the relatives of diabetics, it is usually not in a form suitable for analysis by the heritability model – where age-specific prevalance, current ages (and preferably also onset ages if affected) of patients and of their relatives are required. Indeed for any genetic disease with a variable age of onset, data on onset and current age are necessary for a complete genetic analysis. Lack of details on these topics, or their omission in analysis, has vitiated the results of much of the earlier work on the genetics of diabetics.

The genetic relation between the early-onset and late-onset forms of diabetes is fundamental in the genetic analysis. The methods to resolve this question using data on onset age are therefore

described in detail. Our general conclusion from the results, within the limits imposed by the material and methods available, is that early-onset and late-onset diabetes are largely the same genetic disease. That is, in terms of the liability model, they derive from a common distribution of liability to the disease, or from a highly correlated bivariate distribution.

This conclusion differs from that of Falconer (1967) and Simpson (1969) on analysis of Canadian data. They found lower genetic correlations between onset ages and concluded that early-onset and late-onset diabetes were partly or wholly different genetic entities. Their analysis of the onset age data was not as complete as the method given here and so the Canadian data (Simpson 1969, appendix tables 1–12, 14–17) have been re-analysed by the present methods. Two deficiencies in the data are (1) that the population frequencies were estimated from one section of the Canadian population and this may not have been representative of the whole population, and (2) that patients on diet treatment may not have been ascertained while relatives on diet treatments would be included. With the 'separate' model, which assumes that early and late onset groups

Table 11. *Reanalysis of onset-age data on Canadian diabetics from Simpson* (1969)

(1, Details of the control population; 2, genetic parameters estimated by the cumulative model (diagonals–heritability; off-diagonals (bold type) – genetic correlations).)

Control population

Onset-age group	No. affected, Current-age group 0–19	20–39	40+	Total no.	% affected
0–19	43	31	12	105,974	0·081
20–39	—	41	77	57,317	0·205
40+	—	—	822	34,289	2·400

Genetic parameter estimates

Patient onset-age group	Relatives onset-age group 0–19	20–39	40+
0–19	0·67 ± 0·03	**1·01** ± 0·03	**0·59** ± 0·02
20–39	**0·71** ± 0·04	0·43 ± 0·02	**0·82** ± 0·04
40+	**0·35** ± 0·05	**0·79** ± 0·03	0·26 ± 0·02

are genetically distinct ($r_G = 0$), genetic correlations between onset-age groups were all significantly different from the expectation of zero, and so the separate model again appears untenable. The results for the 'cumulative' model, which assumes that the early- and late-onset groups are genetically similar ($r_G = 1{\cdot}0$), are given in Table 11. Note that, in this analysis, the mean liability of patients in each onset group depends on the proportions (and liabilities) of patients in earlier onset groups. In Table 11 there is a strong trend in heritability with age, the heritability decreasing sharply as onset age rises. This trend has been characteristic of all the analysis on age groups except for the analysis of onset age in the Edinburgh data. The genetic correlations between onset groups in Table 11 are all higher than those given by Simpson (1969) and have a pattern similar to the results in the Edinburgh analyses (Tables 6, 7). As before the genetic correlations from early-onset patients and late-onset relatives were higher and should be more reliable than those in the reverse situation, where biases due to mortality and ascertainment may be more important.

Thus it appears that the Canadian data also support the conclusion that early-onset and late-onset diabetes are largely the same genetic disease, for there is considerable overlap in the genetic liability to early-onset and late-onset disease.

The results from the analysis of current-age groups have already been discussed and compared with the Canadian results. The Edinburgh estimates of heritability tended to be somewhat higher (and more variable since there was less data available) than the Canadian estimates, but both sets of estimates showed a decline in heritability with increasing age group. The anomaly in the genetic correlation of liability between sexes, estimated from the brothers of female diabetics in the Canadian data, was not found in the Edinburgh analysis and is likely to have been a spurious effect.

The range in the heritability estimated from different kinds of relatives is perplexing and difficult to explain or discount. One of the reasons for including a series of relatives in the Edinburgh analyses, was to test the suitability of the heritability of liability model for all classes of relatives, with different genetic and environmental contributions to liability in common. Despite many further investigations we have no satisfactory explanation for the set of results obtained. These anomalies must throw some doubt on the validity of the liability model for diabetes. However, there seems to be no other genetic model which could adequately explain the set of data obtained on the frequencies of diabetes in relatives. It would be easy to dismiss the problem as due to the inadequacy of the questionnaire material, but our checks found the information reliable. Moreover, the rest of the analyses also depend on the same material. It would seem that only by collecting further material in relatives, and checking it more thoroughly, is this problem likely to be resolved.

In a population study on genetic disease, such as this one, it may be difficult to prevent biases in the data and in the analysis. However, if the biases can be identified their effects can often be discounted. The original Falconer (1965) model is more versatile in analysis of age groups, sexes, etc., than the unbiased versions (Smith, 1970), and has been used throughout this paper. This leads to a slight underestimate of the heritability, the bias being about 5–10 % of the true value. However, this bias will be largely offset in the present analyses by incomplete (90–95 %) ascertainment of diabetics in estimating the population prevalence. A possibly more common bias to heritability estimates in man may come from non-genetic familial effects which make family members more alike. The results on spouses of patients and on spouses of first-degree relatives suggest that non-genetic familial effects, at least those acting after marriage, are not important in the diabetes analysis. Of more importance are the effects of differential mortality of diabetics compared with normal individuals, and of severely affected diabetics compared with all diabetics. It has been shown that either or both of these effects could lead to serious underestimation of the true heritability. They could also, as argued here, affect the genetic correlation in liability between onset-age groups and so lead to a conclusion of genetic dissimilarity for a single genetic disease diagnosed at different ages. However, it was not possible to assess the nature or the extent of differential mortality among diabetics and so the effects of the biases due to mortality cannot be resolved.

SUMMARY

The frequency of diabetes in the relatives of diabetics was measured through an interview questionnaire of some 1367 diabetics attending a diabetic clinic. Data on current age, sex, relationship and other details were obtained for all relatives, and on onset age and treatment for diabetic

relatives. Various checks were made on the verbal information given by the patient about his relatives, and the data proved reliable. Details of population prevalence and morbidity of diabetics were given in an earlier paper (Falconer *et al.* 1971).

The heritability of liability model of Falconer (1965) was used in analysis of the data. Two modified versions of this model are described, for testing the hypotheses (1) that early-onset and late-onset diabetes are distinct genetic entities and (2) that they represent different levels of liability to the same genetic disease. The results from analysis of data on onset age for patients and for their first-degree relatives support the model of a single genetic disease. This indicates that early-onset and late-onset diabetes have the same, or very similar, genetic causation and derive from a single distribution of liability to the disease (or from a highly correlated bivariate distribution). The estimate of heritability of liability from the onset-age data on first degree relatives was $0{\cdot}59 \pm 0{\cdot}03$, and there was no significant trend of heritability on onset age.

Another series of analyses were performed using data on the current ages of patients and of their relatives. The prevalence in spouses of patients and of their first-degree relatives was similar to the population prevalence, at the same age, indicating that environmental effects were not important in causing a raised familial frequency of the disease, or in biasing the estimates of heritability. A detailed analysis by sex and age-class for sibs gave a genetic correlation in liability between sexes of $1{\cdot}0 \pm 0{\cdot}06$, and a significant trend in heritability with age, the heritability estimates declining as current age of the patient increased. Changes with age in both the mean liability and in the non-genetic variance in liability would be required to account for this trend. The estimates of heritability from different groups of relatives were quite variable and are difficult to account for. From sibs and parents, the classes with most affected relatives, the estimates were $0{\cdot}56 \pm 0{\cdot}03$ and $0{\cdot}43 \pm 0{\cdot}06$ respectively. However, from children and from the second-degree relatives the heritability estimates were lower, from 0·19 to 0·38, while from cousins the estimate of heritability was $1{\cdot}02 \pm 0{\cdot}14$ – anomalously high. Several reasons to account for the wide range of heritability estimates obtained are discussed and investigated, but no satisfactory explanation was obtained. The effects of several other sources of bias on the heritability estimates are studied in an Appendix. Differential mortality among diabetics may be an important source of bias, leading to low estimates of the true heritability, but the nature and extent of excess mortality among diabetics has still to be resolved.

We are greatly indebted to Miss J. Henry, B.Sc., who was largely responsible for the collection of the data; to Miss Elaine Smith and Mrs Isabel Glen for data-coding checking and punching; to the Records Officers and physicians in all Edinburgh hospitals; to Mr Robert Mcleod and his staff of the Registrar General for Scotland; and in particular to all the General Practitioners in Edinburgh whose help and co-operation were essential to the study. We also gratefully acknowledge financial support from the British Diabetes Society and Pfizer Ltd.

APPENDIX

Sources of bias in estimating heritability

There are several sources of bias in estimating the heritability of liability from data on population frequency and frequencies in relatives. Two sources of bias in the original threshold model (Falconer, 1965), namely a reduced variance and a skewed distribution in relatives, have already been resolved (Smith, 1970). These cause a reduction in the estimates of heritability by about 5 % of the true heritability value. Mendell & Elston (1971) have shown how to adjust the herit-

ability estimate for the reduction in variance of liability among relatives. In the genetic analysis of onset-age groups in the diabetes data, the reduction in variance among relatives may be more severe, especially if the onset-age groups are small and the heritability is high. However, the bias to the genetic correlation in liability between groups should be small, since both the numerator and the denominator of the expression estimating the genetic correlation will be similarly biased, and so the biases will tend to cancel one another.

The effects of some other sources of bias are examined here in general, and for the diabetes analysis in particular. The nature and extent of the bias can often be quickly appraised and estimated from the simple graphical relationship between the population frequency (q_P), the frequency in relatives (q_R) and the heritability of liability (h^2) (Falconer, 1965, fig. 4, or Smith, 1970, fig. 1).

Non-genetic familial effects

It may be possible to assess and remove any bias due to non-genetic familial effects by estimating the frequency q_{RU} in unrelated family members such as spouses or adopted children. The quantity $(q_R - q_{RU} + q_P)$ would then be used as the frequency in relatives for the heritability estimation. In the diabetes data, the correlations in liability between spouses were low, indicating that common environmental effects, at least those acting after marriage, were not important in biasing the heritability estimates from relatives. There were insufficient data on adopted children to study the effect of a common environment during childhood.

Population frequency estimates

If the estimate of the true population frequency is biased low but the frequency in relatives is unbiased, then the heritability will be overestimated. This can be ascertained readily from the graphs described above. Choosing a value for the frequency in relatives (q_R), it is apparent that as the estimate of population frequency (q_P) falls the corresponding heritability estimate is increased. The reverse holds if the estimate of population frequency is too high.

In the diabetes analysis, the ascertainment of cases in the population was judged to be at least 90 % complete. A deficit of this order in population frequency does not lead to a serious bias in the heritability estimates. For example, choosing a heritability of 50 % and a 10 % underestimate of the population frequency, the estimated heritability would be about 52 % if the true population frequency were 0·1 % and about 54 % if the true population frequency were about 1·0 %. Thus for diabetes, which falls into the range of the example, the estimates of heritability may be too high by about two to four percentage points, due to the incomplete ascertainment of cases in the population.

A different kind of bias may exist because the population frequency and the frequency in relatives were estimated by different methods, and may not be directly comparable. However, the correspondence between the frequency in spouses (obtained from the questionnaire) and the population frequency (obtained by listing all ascertained cases) indicates that a bias due to the method of ascertainment is not likely to be important in the diabetes analysis.

Mortality

If the rate of cumulative mortality among affected individuals (m_A) is higher than that in the population (m_P), this will lead to an underestimate of the true heritability. Let $m = (m_A - m_P)$

measure the excess rate of cumulative mortality. Then the ratio of the frequency in relatives to the frequency in the population is

$$(1-m)q_R/(1-m)q_P$$

Table A 1. *Estimates of heritability with excess mortality (see text), (A) among all affected individuals and (B) among severely affected cases*

True population frequency (%)	Excess rate of mortality (m)	True heritability: 0·20 A	0·20 B	0·50 A	0·50 B	0·80 A	0·80 B
		Estimate of heritability					
0·1	10	0·20	0·18	0·49	0·46	0·78	0·71
	50	0·18	0·17	0·44	0·42	0·70	0·66
	90	0·14	0·14	0·35	0·35	0·54	0·53
1·0	10	0·20	0·18	0·48	0·42	0·78	0·68
	50	0·17	0·16	0·42	0·37	0·66	0·60
	90	0·13	0·12	0·30	0·29	0·46	0·45
10·0	10	0·19	0·13	0·47	0·37	0·74	0·53
	50	0·14	0·12	0·35	0·29	0·55	0·45
	90	0·08	0·08	0·20	0·19	0·31	0·29

and the ratio is unchanged by excess mortality among diabetics. However, it can be ascertained readily from the graphs mentioned above, that a decrease in the population frequency with a constant ratio will lead to a lower estimate of heritability. So the heritability will be underestimated if there is excess mortality among affected individuals. A guide to the extent of the bias is given in Table A 1 for a range of situations. If the excess rate of cumulative mortality (m) is less than 10 %, the bias in the heritability estimates will be fairly small, but as m increases the bias becomes more serious.

The same rate of mortality may not apply to all affected individuals. For example, severe cases are likely to have a higher rate of mortality than mild cases. This may lead to further underestimation of the heritability. An upper limit to the effect of this form of mortality on the heritability estimates can be got by assuming that all those who have died had a liability above a threshold for mortality, while those below the threshold for mortality have survived. Making this assumption and using the same range of situations as before, the resultant heritability estimates were calculated and these are also given in Table A 1. As expected, the biases in the heritability estimates become larger, especially if the excess mortality is low and heritability is high.

In the diabetes analysis it was not possible to separate the excess mortality rate for diabetics from the effects of time trends in frequency of the disease and in detection rates. However, a maximum level of the excess rate of cumulative mortality for diabetics can be estimated from the difference between the observed and the 'potential' age-specific prevalence (fig. 11, Falconer *et al.* 1971). The latter was derived by accumulating the current detection rate at each age up to the age concerned. The difference between the observed and potential age-specific prevalence would indicate a maximum excess rate of cumulative mortality for diabetics of about 30–50 % from ages 30 to 60 rising to 70–80 % over age 65. The true heritability estimates would then be underestimated, especially in the later age-groups. Thus taking the observed population frequency for diabetes (0·63 %) and an excess rate of cumulative mortality of about 50 %, an estimated heri-

ability of 50 % would represent a true heritability of about 61 %. Mortality is likely to be higher among cases with higher liability. Early-onset cases have a higher liability than late-onset cases, and they are clinically more severe. They will also have a higher cumulative mortality than any age since they have had the disease longer. The excess mortality may also be higher in those with a large genetic (permanent) contribution to liability whereas a large environmental contribution (e.g. nutritional) may be modified after diagnosis. All these factors could lead to the excess mortality being among diabetics with high genetic liability and thereby the true heritability would be further underestimated. If the difference between the observed and potential age-specific prevalences were due to mortality of severe cases, using the same figures as in the previous section, the true heritability would be 67 % instead of estimated value of 50 %.

These results represent the maximum bias in the heritability estimates due to excess mortality among diabetics. In practice the biases are likely to be much smaller. However, it will not be possible to assess their extent until the nature and extent of the excess mortality among diabetics is resolved.

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Correlation in Liability Among Relatives and Concordance in Twins

Further Results

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Abstract. The expected frequency among relatives of ascertained individuals for a threshold trait with multifactorial inheritance is presented for the upper range of population frequency. Expected values of various measures of concordance in twins are also derived.

Key Words
Liability
Multifactorial
Twins
Concordance

In an earlier paper [SMITH, 1970] the expected frequency of a disease among relatives of affected individuals was derived for threshold traits with multifactorial inheritance. In response to numerous requests, the results are extended here to cover the upper range of population frequency. The results for alternative measures of concordance in twins are also considered.

Frequency among Relatives

Using the same model and methods as previously [SMITH, 1970] the expected frequency of a trait in relatives of individuals with the trait was derived for the upper range of population frequency. The results are presented graphically in figure 1. The frequency in relatives for traits with a population frequency (P) of more than 50% cannot be derived from the corresponding results for (1—P) and so are also presented. The results in figure 1 can also be derived by numerically integrating over phenotypic rather than genetic classes of individuals with the trait; taking into account the frequency of the phenotypic class, the expected genetic value of relatives and their residual variance about this mean.

The original formula of FALCONER [1965] for estimating the frequency of a trait in relatives can provide a good approximation to the results in figure 1,

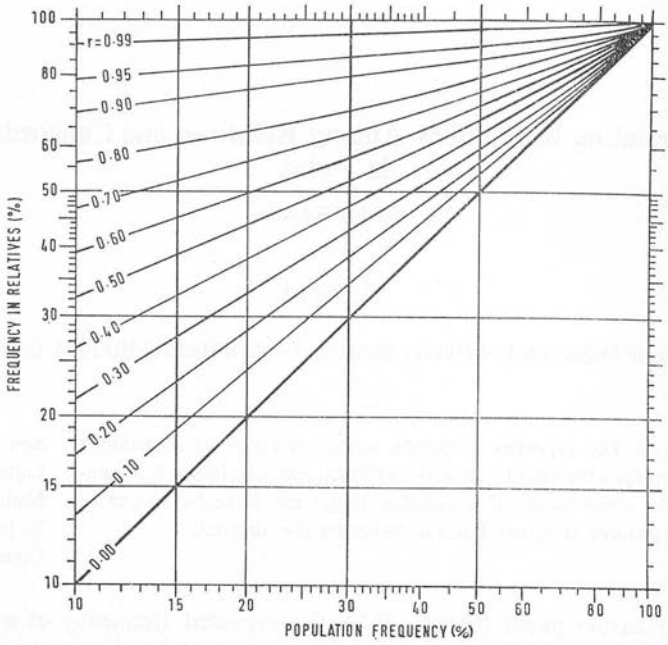

Fig. 1. The correlation (r) in liability between relatives, given the population frequency, and the frequency in relatives of individuals with the trait.

if it is modified to take into account the reduced variance in relatives of individuals with the trait [MENDELL and ELSTON, 1971; REICH *et al.*, 1972]. The approximation is:

$$r = \frac{x - x_r \sqrt{(1 - r^2 a(a-x))}}{a}$$

where r is the correlation between relatives, a and x refer to the mean deviate and threshold value for individuals with the trait, and x_r refers to the difference between the threshold and the mean liability for relatives. This approximation is accurate over a wide range of situations, to within 1% of the expected values in figure 1.

Two further developments of the multifactorial model have been the estimation of recurrence risks [SMITH, 1971a; CURNOW, 1972], and the use of bivariate and multivariate normal distributions with maximum likelihood in analysis and resolution of genetic disease [MENDELL and ELSTON, 1971; REICH *et al.*, 1972; THOMPSON, 1972].

Twin Concordance

The twin concordance rate given by SMITH [1970] is the so-called proband concordance rate (ALLEN *et al.*, 1967]. Other measures are also used in the literature, depending on the mode and level of ascertainment, so it may be useful to show when these may be appropriate and to relate them to one another.

Consider all twin pairs in a population with individuals classified as *1* if they have the trait and *0* if they do not. Let P_{11}, P_{10}, P_{01} and P_{00} represent the proportions of the four types of pairs, namely *11*, *10*, *01* and *00*. The population frequency P is the equal to $P_{11}+P_{10} = P_{11}+P_{01}$.

If ascertainment is through the trait, twin pairs of type *00* will not be ascertained and pairs of type *11* may have a higher probability of ascertainment than types *10* and *01*. This bias in ascertainment can be avoided if the *individual* rather than the twin pair is considered the unit of ascertainment and the twin pair is counted once for each member individually ascertained. This is the *proband* concordance rate (P_P) and is given by

$$2\pi P_{11}/(2\pi P_{11} + \pi P_{10} + \pi P_{01})$$

which does not depend on the ascertainment probability (π). P_P is identical to the segregation probability [MORTON, 1969] for twins.

Another measure of concordance often used is the proportion of concordant sets among ascertained twin pairs, called the *pairwise* concordance rate (P_W). The probability of ascertainment is π for *10* and *01* pairs, but is $(1-(1-\pi)^2)$ for *11* pairs so P_W is:

$$P_{11}(1-(1-\pi)^2)/(P_{11}(1-(1-\pi)^2) + \pi(P_{10}+P_{01}))$$

and depends on the ascertainment probability. If all twins with the trait are ascertained ($\pi = 1$), P_W reduces to $P_P/(2-P_P)$, so the different expressions for concordance can be derived from one another and from figure 1.

If the ascertainment is not associated with the trait being studied, all types of twin pairs have an equal chance of being included in analyses and there is no ascertainment bias. The proband (P_P) and pairwise (P_W) concordance rates then apply as before. Another possible measure of concordance is the proportion of *11* and *00* concordant pairs (P_T), namely $P_{11}+P_{00}$ which equals $1-2P(1-P_P)$. This will be called the *total* concordance rate and may be used when the frequency of the trait in the population is intermediate.

These various measures of concordance will usually be adequate for summarising observed data on twins in human genetics. More exhaustive and efficient methods for estimation of the basic parameters are, of course, available [TALLIS, 1962].

Interpretation of Concordance Rates

Interpretation of the observed twin concordance rate for a trait directly into genetic terms is usually not possible, unless inheritance is fairly strictly Mendelian so that monozygous (MZ) concordance rates close to 100% are obtained. Even when combined with information on other relatives, concordance rates are unlikely to be diagnostic in determining the mode of inheritance of a particular trait [SMITH, 1971b]. If multifactorial inheritance is assumed, the relation of the concordance rate to the underlying correlation in liability between twins is useful since the correlation, unlike the concordance rate, does not depend on the frequency of the trait in the population. Further interpretation of the correlation into the heritability of liability depends on several factors, such as the absence or allowance for environmental effects common to members of a twin pair and as the absence of substantial non-additive genetic variation.

An 'index of heritability' proposed by HOLZINGER [1929], from concordance in monozygous and dizygous twins, has been widely used in human genetics. However, the genetic interpretation of this index is unclear, and its value depends on the population frequency for the trait. For these reasons, it is not a satisfactory index of heritability and its use should be discontinued [CAVALLI-SFORZA and BODMER, 1971].

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A statistical and genetical study of diabetes

III. Empiric risks to relatives

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The previous papers in this series dealt with the prevalence and morbidity of diabetes in the population and with the estimation of the heritability of liability assuming multifactorial inheritance. The same sets of data are used here to estimate empiric risks for relatives of diabetics – that is, the observed frequency of diabetes in relatives of diabetics. There are many complications in the analysis arising chiefly from the variable age at onset of the disease, differential mortality of diabetics, changes in detection rates over time and limits on the partitioning possible with the data. Various methods of estimating the empiric risks are examined and the risks derived from them are presented and compared.

MATERIAL AND METHODS

Material

The data used in the analysis are described in detail in the second paper of the series (Smith, Falconer & Duncan, 1972). Briefly they consist of information on 25,635 relatives of 1367 living diabetics (referred to throughout as the patients or probands), obtained through an interview questionnaire of patients attending a diabetic clinic. Data were available on the sex, current age and onset age of patients and on sex, relationship, current age (or age and year of death) of the relatives and on onset age if the relative was affected. Onset age was taken as the age at clinical diagnosis of diabetes.

Variable age of onset

For diseases with variable age at onset estimation of empiric risks from a set of data is much more complex than for conditions manifest at birth or early in life. The age at onset of the proband and of affected relatives must be taken into account and the risks of manifesting the disease by successive ages, as well as the total risk, will usually be required. In addition, the family history of the disease may increase with time, so that empiric risks calculated from data with the current family history will tend to underestimate the actual risk. These two problems arising from variable onset age are considered first.

Risk curve

For conditions with variable age at onset, the risk of ever manifesting the condition increases with length of life and will take the form shown in Fig. 1. This represents the proportion of individuals in the population affected by a specified age and so the risk curve will be an increasing function with age. The risk curve will plateau (dotted line) only if no further cases manifest after a certain age. If an individual is not yet born, the risk R of becoming affected by a certain

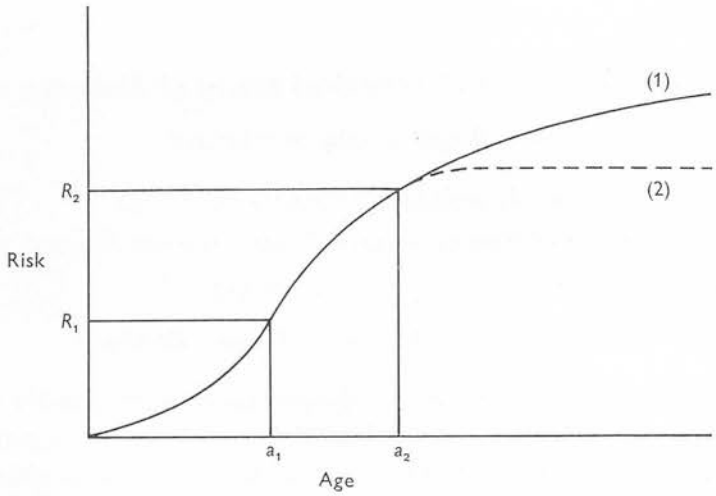

Fig. 1. Graph showing how the risk of ever being affected increases with length of life if individuals may succumb to the disease at any age (1) but will plateau (2) if no individuals succumb to the disease after a given age.

age can be read directly from the graph. But if the individual is a certain age a_1 and is still unaffected, his risk of yet becoming affected by age a_2 is conditional on being unaffected at age a_1 and is given by

$$(R_2 - R_1)/(1 - R_1),$$

where R_2 and R_1 are the unconditional risks at ages a_1 and a_2 respectively.

Change in family history

Empiric risks for a specified family history can be obtained from collected data. These measure the observed proportion of relatives affected at each age for a family history corresponding to that of an individual *at the time* of estimating the risk. However, the family history may change with time if other relatives become affected and then the individual's actual risk would be higher than that estimated from the data. For example, a child at birth may have only a father affected. The risk at each age could then be calculated as the proportion of individuals with an affected father who were affected at each age. But this would exclude individuals who at birth had only a father affected but who subsequently had other relatives become affected; the risk for this excluded category would be higher than for the others. Thus the risks calculated for a specified family history may be too low. However, they provide a lower bound for the risk estimate. They will be called the S risk estimates since they refer to specified family histories. In some families the family history may decrease with age as further members are born, but the *average* risk of all families will increase with time due to the increase in prevalence with age.

An upper bound for the risk estimate can similarly be obtained by including families with *at least* the specified family history at each age. These will be called the A risk estimates since they refer to all families with the specified family history or worse. The actual risk will lie between these two extremes, its position depending on the length of the period between the age at estimation and the age to which the estimate applies (See Appendix).

Table 1. *Form of tables used in calculating empiric risks to relatives of diabetic patients (the probands) with current age-group (i) and onset age-group (j)*

		Current age-group (k) of relatives					Proportion affected during each onset age group
		1	2	3	4	5	
Total in age-group (k)		N_1	N_2	N_3	N_4	N_5	—
Average age		a_1	a_2	a_3	a_4	a_5	—
Onset age-group (l) of affected relatives	1	a_{11}	a_{12}	a_{13}	a_{14}	a_{15}	q_1*
	2	—	a_{22}	a_{23}	a_{24}	a_{25}	q_2
	3	—	—	a_{33}	a_{34}	a_{35}	q_3
	4	—	—	—	a_{44}	a_{45}	q_4
Total affected		A_1	A_2	A_3	A_4	A_5	—
Proportion affected		P_1	P_2	P_3	P_4	P_5	—

* $q_1 = \left\{\frac{a_{11}}{t_1} + \sum_{l+1} a_{1k}\right\} \Big/ \Sigma_l N_k$, where $1/t_1$ is a multiplication factor to adjust the numbers in the diagonal cells (see text).

Tabulations

The basic form of the tabulations made in the analyses is given in Table 1. For affected individuals with current age-group (i) and onset age-group (j), relatives can be allocated by current age-group (k) and if affected, by onset age-group (l). This table for relatives corresponds closely to Fig. 3 in Falconer, Duncan & Smith (1971) for analysis of the age distribution of living diabetics in the population. The reader is referred to that paper for a full description of the table and its implications. The derivation and composition of the various estimates of prevalence in relatives will be discussed below.

Partitioning

Although the data on relatives appears extensive, the amount of partitioning possible is quite restricted, otherwise there would be many empty cells in the tables or cells with small numbers which would give rise to unreliable risk estimates. Thus in the tabulations the data were pooled wherever possible. Relatives with the same degree of relationship were combined, sexes were pooled and the current age (i) of the proband was ignored. The number of age-groups for classes j, k and l (in Table 1) must also be restricted. As in the previous paper, four age-groupings (0–24, 25–44, 45–64 and 65–84) were chosen and these correspond to numbers 1, 2, 3 and 4 in Table 1. Age-group 5 in Table 1 contains relatives whose current age was 85 or over.

As discussed in the first paper (Falconer *et al.* 1971), the diagonal cells in Table 1 will underestimate the proportion of individuals becoming affected during the age-group. This is because individuals may yet become affected before they pass out of the cell. It is possible to adjust for this deficiency by estimating the proportion (t) of the possible duration in the cell that individuals have already attained. This is simply the average number of years so far spent in the cell divided by the total range in the age-group. Multiplying the numbers in the diagonal cells by $1/t$ will thus adjust for the deficiency. For example, if the average age is at the mid-point of the cell, the multiplication factor will be 2. In the first paper this factor was found to be too high, because it referred to 1-year age-groups and ascertainment was not instantaneous but

spread over 1 year. This bias should be unimportant in the large age-groups used here but these introduce another bias. The chance of becoming diabetic increases with age and a larger number of individuals will become affected in the second half of a cell than in the first half. Thus despite adjustment for the average age attained in the cell, the number of individuals becoming affected during an age-group may still be underestimated.

Cumulation

Individuals may be counted in more than one cell of the tables. This will be called cumulation and it serves to increase the numbers in the early age cells of the tables. That is, an individual can be counted in all age-groups up to and including his current age, and his diabetic status at each age can also be taken into account. However, although cumulation greatly increases the numbers, especially in the early age-groups, the composite nature of the figures makes them hard to interpret and they are affected by trends in detection rate, differential mortality of diabetics and other factors. Thus cumulation was not used in the main analyses, but only where numbers were very small as with two or three affected relatives.

Frequency reduction

In the first paper of the series (Falconer *et al.* 1971) it was shown that the frequency of living diabetics in any onset-age class decreased with increasing current age. This was called frequency reduction. The actual prevalence of living diabetics was shown to be substantially less than the estimated potential prevalence, the expected prevalence if there was no frequency reduction. The causes of frequency reduction were thought to be differential mortality of diabetics, changing detection rates or changes in the frequency of the disease with time. However, since only living diabetics were ascertained, it was not possible to measure the relative importance of each effect. Frequency reduction will also affect the observed frequencies for relatives and will result in underestimates in empiric risks derived from them. Much of the work in this analysis was to derive empiric risks which would minimize the effects of frequency reduction.

Differential mortality

At interview patients were questioned about their relatives in a systematic way and information on both living and dead relatives was recorded. From the difference in frequency between living and dead diabetics it is possible to estimate the differential mortality due to diabetes. The logic for this estimation is given in Falconer *et al.* (1971) (pp. 362–3) and is summarized as follows. The frequency of diabetes in a given onset-age/current-age cell after a duration d years of disease in the cell can be written as

$$q_d = q_0 k^d,$$

where q_0 is the frequency of all diabetics in the cell and k is the rate of survival of diabetes over a 1-year period relative to all individuals in the same cell. Because of age-grouping, each cell of the derived tables contains individuals with a range of current age and a range of onset ages for those who are affected. The mean duration d of life of all diabetics while in the cell can thus be estimated. Then q_d is estimated as the frequency of living diabetics among living relatives and q_0 by the frequency of all diabetics among all relatives in the particular cell. Because the comparisons are made within cells and involve the same set of individuals the estimates of differential mortality are largely independent of detection-rate changes and of trends in disease

Table 2. *Estimates of empiric risks*

Estimate	
	USING CURRENT AGE OF RELATIVES
	Living relatives
1	Proportion affected in each current age-group, interpolated or extrapolated to the top age of the age-group.
2	Proportion affected in each current age-group, adjusting the numbers in the diagonal cells of Table 1 for average attained age.
3	Multiplication of (1) by the ratio of potential to actual prevalence from Falconer *et al.* (1971).
	All relatives (dead relatives – death at age m years, n years ago)
4	As for (1) but taking current age of dead relatives as $(m+n)$.
5	As for (1) but taking current age of dead relatives as (m).
6	As for (5) but including dead relatives only if $(m+n)$ is less than the top age of the age-group.
	USING ONSET AGE OF RELATIVES
	Living relatives
7	Proportion affected in diagonal cells of Table 1, adjusted to the top age of the cell and summing over onset age-groups.
	All relatives
8	As for (7) but including dead relatives if $(m+n)$ is less than the top of the cell.
9	As for (8) but including also the non-diagonal cells for each onset age-group and summing over onset age-groups.

frequency. The variance of the estimate of k, the annual differential mortality of diabetics, is given by

$$V_k = \frac{k^2}{d^2}\left(\frac{1}{A_d}+\frac{1}{A_0}\right),$$

where A_d and A_0 are the number of living and the number of all diabetics respectively in the cell.

Estimators of empiric risks

Because of variable onset age, frequency reduction and differential mortality, simple empiric risk estimates may suffer from several serious biases and deficiencies. The interplay and complications of the various factors make the analyses very involved and difficult to describe. The object of the next section is to consider in turn a series of different empiric risk estimators showing how they are derived, what their deficiencies are and how they attempt to remove the biases of other estimates. They are summarized in Table 2. In the first section the estimates are derived independently for each current age-group, while in the second section the estimates depend on onset age-groups and include the sum of the estimates for previous onset age-groups. Note that only living diabetics were ascertained. If those who died were the more severe cases with more relatives affected, the empiric risks will be underestimated. Since probands were independently ascertained, the effects of variable family size can be ignored, except when the risks in families with two or more affected persons are considered. A complication in the analysis was the fact that in about 10 % of cases, the onset age of the diabetic relative was not given. To include these in the analysis, they were allocated to appropriate onset age-groups in proportion to the numbers with known onset age.

Current age-groups; living relatives

The simplest estimates of empiric risks in relatives are given by the frequency of diabetes in living relatives. These estimates will underestimate the true empiric risks only if there is

differential mortality of diabetics, because all living individuals will be exposed to the current detection rate and current disease level in the population (it is assumed that these are not decreasing). Estimates of prevalence in living relatives can be derived simply by calculating the proportion affected in each current age-group; that is, $P_k = A_k/N_k$ in Table 1. This is the frequency at the average age of the group. To compare the various risk estimates with one another, the risks will all be expressed at the age for the upper boundary of the age-group. This was found for the present case simply by drawing the risk curve and interpolating or extrapolating to the top age of the age-group.

Since new cases can only fall in the diagonal cells of Table 1 an alternative to interpolating or extrapolating to the top of the group is to adjust the numbers in the diagonal cells for attained age, as already described. These can then be added to the numbers in the other cells of a column to obtain an estimate (2) of the empiric risk at the upper age of the age-group. This may lead to overestimates of the empiric risk if detection rates have increased recently since cases which were undetected previously now all fall into the diagonal cells.

It is possible to adjust for frequency reduction in living relatives by using the ratio of the estimated potential population prevalence to the observed population prevalence of diabetes, as given in Fig. 2 (Falconer *et al.* 1971, fig. 11). The estimate (1) can thus be multiplied by this ratio, for the appropriate age-group, to provide an estimate (3) which gives an indirect estimate of the potential prevalence in relatives of diabetics.

Current age-groups – all relatives

If there is differential mortality of diabetics, then dead relatives should also be included in estimation of empiric risks in relatives. However, their inclusion introduces other complications in the analysis. Suppose a relative died at age m some n years ago. There are several ways this information could be used and each will give a somewhat different estimate of the empiric risk in relatives. The current age of a dead relative could be taken as $(m+n)$, the age he would be if he had lived. The estimate (4) derived in this way will give an underestimate of current empiric risks, since relatives who are dead are not exposed to current detection rates and disease levels, and some who were unaffected at death might have been affected if they were alive today. Another estimator (5) can be derived by considering age at death as the current age, that is putting n equal to zero. If there is differential mortality of diabetics, affected relatives will tend to die in lower age-groups than normal relatives, so the empiric risks at the lower ages would be overestimated. A third alternative is to include only those dead relatives who would still be in the same age-group if they were alive today, so that $(m+n)$ is less than the upper boundary for the age-group. This estimate (6) will provide better estimates of frequency in the diagonal cells of Table 1 but will underestimate the frequency in the off-diagonal cells since dead individuals cannot pass to other cells while living relatives can.

Onset age-groups

Falconer *et al.* (1971) used data on onset-age/current-age groups in the population to estimate the potential prevalence of diabetes, the estimated prevalence if there was no frequency reduction. The same methods cannot be used here to estimate potential empiric risks because of the small number of affected relatives available. However, other estimates of the potential empiric risks in relatives can be derived. These depend on the *summation* of frequencies in relatives over onset age-groups.

Table 3. *Estimates of differential annual mortality* (*per* 1000) *of diabetics* (*with standard errors in parentheses*)

Onset age	Current age 0–24	25–44	45–64	65–84	84+
0–24	18 (3·7)	8 (0·8)	70 (41·2)	—	—
25–44	—	5 (1·7)	31 (0·6)	53 (5·3)	—
45–64	—	—	33 (0·9)	51 (0·8)	197 (38·2)
65–84	—	—	—	42 (3·3)	81 (61·9)

The simplest potential empiric risk estimate is from living relatives. For example, estimate (7) uses the proportion affected in the diagonal cells of Table 1, adjusted for attained age to the top of the cell, and summed over age-groups. As before, this estimate will be biased if there is differential mortality of diabetics. The bias can be eliminated by including dead relatives only if they would still be in the same cell of the table if they were alive today (i.e. at time of survey, 1968); that is, if $(m+n)$ were less than the top age of the cell. This estimate (8) uses only the diagonal cells of Table 1. Another estimate (9) calculated as (8) but using all the cells of the table can also be derived. Though this reduces the sampling errors of the estimates by including more relatives, it reintroduces some of the biases due to frequency reduction.

All of these estimates are liable to some deficiencies or drawbacks and it is unlikely that a completely unbiased estimate of the empiric risks could ever be derived with so many complicating factors. Among the various estimates described (and undescribed), estimate (8) is considered to be the one most free from the various biases considered. Its disadvantage lies in that it uses only a proportion of the relatives recorded so the sampling errors will be larger than for some of the other estimates, and these will accumulate with the summation over onset ages. The one bias that estimate (8) may suffer from is through recent increases in detection rate, which will give a temporary excess of diabetics in the diagonal cells. In general, the estimates (8) are considered to provide the best estimates of the empiric risks in relatives and correspond most closely with the population potential prevalence of Falconer *et al.* (1971).

Two or more affected relatives

Estimating empiric risks when two or more relatives are affected introduces further complications in analysis. The number of useful families was reduced to 40% of the original set, so numbers were more restricted. Partition of the data into four groups for each affected individual was no longer feasible and onset groups 0–44 and 45–84 were chosen. The relationship of each relative to the proband was known but the relationships *inter se* would be difficult to deduce. To avoid this complication, the empiric risks with two or more affected relatives were therefore only estimated for sibs of probands. Finally to increase the numbers in the table, relatives were included in more than one cell where possible, as explained in the section on cumulation.

RESULTS

Before giving the results on empiric risks, the analysis of differential mortality in diabetics is presented, since differential mortality is one of the factors which affect the estimates of empiric risks.

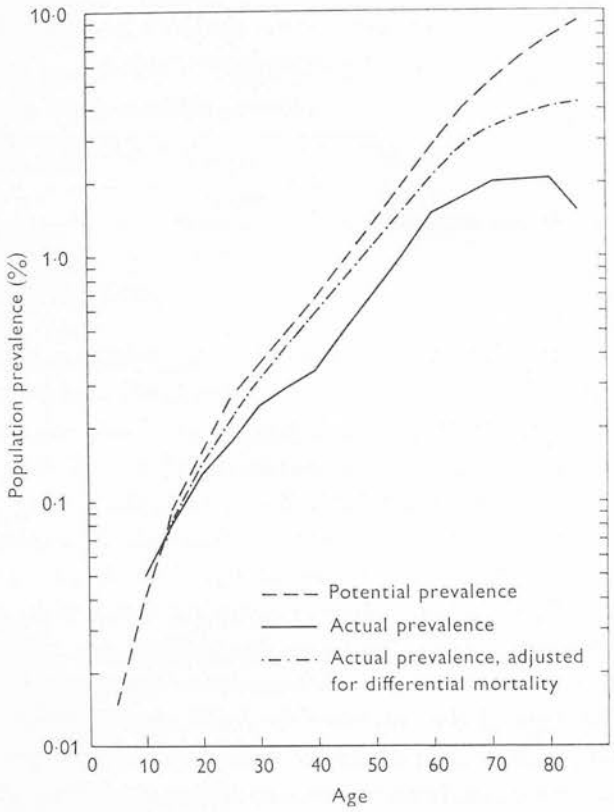

Fig. 2. Contribution of differential mortality of diabetics to the difference between the potential and the actual population prevalence.

Differential mortality

Estimates of the differential rates of mortality among diabetics are given in Table 3, for the various current-age/onset-age groups. The estimates show that the annual differential mortality tends to increase both with onset age and with the duration of the disease, rising from 1-2% per year for groups under 40 years to 3–5 % for groups over 40 years. The increase with onset age in differential mortality of diabetic relatives agrees with the results estimated from the frequency reduction among diabetics in the population (Falconer *et al.* 1971). Of course, though late onset cases may have a higher annual differential mortality than early onset cases, the cumulative differential mortality of early onset diabetics will be much higher by a given age than for late onset diabetics.

Knowing the extent of differential mortality, its contribution to the difference between the estimated potential frequency (if there were no frequency reduction) and the actual frequency can be assessed. Taking the potential frequency and the rate of differential mortality at each age, the frequency expected if mortality alone were involved can be derived. The results are shown in Fig. 2. It appears that only part of the difference between actual and potential prevalence is due to differential mortality. This was expected since it is well known that there has been an increasing trend in morbidity from diabetes over the last two decades (Hayward & Lucerna, 1965).

Table 4. *Comparison of empiric risks (estimate 2) in living first-degree relatives (A) with at least one first-degree relative affected and (S) with only one first-degree relative affected*

Proband onset		Empiric risks (%) of diabetes in living first-degree relatives at age: 25	45	65	85*
0–24	*A*	7·1	8·1	7·4	9·1
	S	8·3	8·6	4·4	6·7
25–44	*A*	(1·7)†	2·0	8·1	13·3
	S	(0·4)†	1·3	2·2	12·3
45–64	*A*	0	(0·5)	10·4	16·7
	S	0	(0·4)	6·4	13·6
65–84	*A*	—	(1·4)	7·3	16·7
	S	—	(1·1)	(5·9)	13·4

* Risks extrapolated to age 85. Also Tables 5–7.
† Less than five affected relatives. Also Tables 5–7.

Changing family history

At any particular stage individuals at risk will have a specific family history but this family history may change with time. Empiric risks can be estimated for a specific family history (*S*) or for families with at least the specified family history (*A*). The appropriate risk at any age will depend on the possible change in family history with time and will lie between the *S* and *A* empirical estimates. Comparison of these estimates is most easily made among living relatives (but including dead relatives in the relevant family history). The empiric risks from estimate (2) are given in Table 4 for first degree relatives. As expected, the *A* empiric risks are generally higher than the *S* empiric risks, the modal value for their ratio being about 1·3. For short time-intervals over which the risk estimates are given, the appropriate empirical risks will be closer to *S*. But for longer time-intervals, and possible changes in family history, the appropriate empirical risks will be intermediate between the *A* and *S* estimates. The *A* tables contained about 1·55 times as many individuals as the *S* tables, so the risks to those with *more* than the specified family history (one first-degree relative affected) can be estimated and were found to be about 1·85 times the *S* estimates. In the subsequent tables the risks will be given for the *A* tables only since they contain the most data and apply to a wider class of families.

Risk estimators

The various estimators of empiric risks, listed in Table 2, can now be compared. Their derivation and possible deficiencies have already been described and the latter can be examined in practice here. To make the different estimates all directly comparable, the risks are given for being affected by a certain age; 25, 45, 65 or 85 years respectively.

The simplest risk estimates are those derived from the current age-groups for living relatives. Estimate (1) was derived from these by interpolating the risk curve from the average age in the group to the top age of the group, while estimate (2) for each age was derived by adjusting the number of diabetics in the diagonal cell for the average attained age in the cell and adding it to the other cells in the group (Table 1). Estimate (2) tended to give the higher risk estimates (Table 5). This arises because there are more diabetics in the diagonal cells than would be expected from the numbers in the other cells and this results from the frequency reduction in

Table 5. *Various estimates of empiric risks in first-degree relatives of probands*

		Empiric risks (%) by age:			
		25	45	65	85
Population prevalence					
Living diabetics		0·18	0·47	1·68	1·37
Potential prevalence*		0·24	0·86	3·80	9·20
Proband onset	Estimate†				
0–24	1	4·7	5·2	5·4	7·0
	2	7·1	8·1	7·4	9·1
	6	5·1	6·2	6·7	7·5
	8	7·6	12·6	17·4	25·2
25–44	1	(1·3)	2·8	6·6	13·0
	2	(1·7)	2·0	8·1	13·3
	6	2·1	4·3	0·9	11·7
	8	(1·7)	(2·3)	10·4	19·3
45–64	1	—	(1·4)	8·0	13·0
	2	—	(0·5)	10·4	16·7
	6	(1·1)	2·9	9·5	15·4
	8	—	(0·3)	9·9	20·1
65–84	1	—	(1·6)	6·0	15·0
	2	—	(1·4)	7·3	16·7
	6	(1·8)	2·6	6·0	11·8
	8	—	(1·4)	8·1	22·0

* Falconer *et al.* (1971) (Fig. 11).
† See Table 2.

the other cells. As there is differential mortality, these estimates from living relatives will underestimate the actual risks to relatives. To adjust for the frequency reduction, which includes differential mortality of diabetics, estimate (3) was derived from estimate (1) by multiplying the ratio of potential to actual population prevalence at each age. The risk estimates derived in this way were all very much higher than any of the other risk estimates, especially at the higher ages, so estimate (3) does not seem appropriate.

The next set of estimators dealt with current age-groups for all relatives cited, that is including dead relatives. The basic difficulty with including dead individuals is that they remain in the cells in which they died while living relatives move on to other cells. The risk estimators can consider their current age as (4) that which they would have had if they were alive at the time of the survey or as (5) the age at death, including all dead relatives or (6) can include dead relatives only if they would still be in the same cell as that in which they died. All the estimates are biased, but in different ways as explained earlier. The results for estimate (6) are given in Table 5 and are quite similar to those from living relatives but, as expected, tend to be higher for the low age-groups and lower for the high age-groups.

The final set of estimates was derived by summing the frequencies over onset age-groups, to give the potential prevalence in relatives. Estimate (8) was considered to be most free from the biases previously discussed by dealing with all cited relatives in the diagonal cells, adjusted for the average attained age in the cell. The risks derived by estimate (8) were usually higher than the risks estimated from current age-groups and especially so for the higher ages (Table 5). This was confirmed by the results from estimate (9) which includes all cells in the tables of relatives. Thus, as in the analysis of population frequency, the risks to relatives estimated from current

Table 6. *Empiric risk estimates* (8) *in first-degree, second-degree and third-degree relatives of probands*

Proband onset	Degree of relative	Empiric risks (%) by age: 25	45	65	85
0–24	1	7·6	12·6	17·4	(25·2)
	2	—	(2·1)	(3·5)	(5·7)
	3	(0·5)	(1·0)	(3·6)	(3·6)
25–44	1	(1·7)	(2·3)	10·4	19·3
	2	1·1	(1·9)	5·9	(9·2)
	3	(1·3)	(2·9)	8·0	(16·9)
45–64	1	—	(0·3)	9·9	20·1
	2	—	0·8	(1·7)	(4·8)
	3	—	—	2·8	9·6
65–84	1	—	(1·4)	8·1	22·0
	2	—	(0·5)	(2·5)	(16·4)
	3	—	—	(2·8)	(9·9)

ge groups were much lower than the estimated potential empiric risks, which sum the risks ver onset age-groups. In general, the estimates (8) are considered the best estimates of the mpiric risks in relatives and correspond most closely to the population potential prevalence f Falconer *et al.* (1971).

irst-degree relatives

The pattern of the empiric risks for first-degree relatives as given in Table 5 is interesting. Early onset probands have a high frequency of early onset relatives. But the percentage of elatives affected by ages 65 and 85 are similar for all onset age-groups of probands. Thus the ifetime empiric risks for first-degree relatives are the same for families with probands of different onset ages. These estimated potential lifetime risks are about twice the estimated population potential risk and more than ten times the observed population prevalence of living iabetics.

econd- and third-degree relatives

The pattern of empiric risks in first-degree relatives is compared with those for second- and hird-degree relatives in Table 6. As expected the risks are lower than for first-degree relatives. However, the potential prevalence in second- and third-degree relatives is lower than the stimated population potential prevalence in half of the cases. Another anomaly is that third-egree relatives (cousins) tend to have a higher frequency of affected than do second-degree elatives, as already noted in the heritability analysis. Finally, the high frequency of early nset relatives in early onset patients is not found in the second- and third-degree relatives.

wo affected relatives

The empiric risks to sibs of probands with at least one other relative affected are given in Table 7. Despite using only two onset age-groups and cumulation (counting individuals in more than one cell where possible), the numbers were rather small and the empiric risks are quite variable. In general, the risks are substantially higher than for one relative affected.

Table 7. *Empiric risk estimates* (5) *for individuals with a sib affected* (*the proband*) *and at least one other relative affected*

Sib (proband) onset	Other relative		Empiric risks (%) by age:			
	Onset	Degree	25	45	65	85
0–44	0–44	1	5·1	10·0	24·0*	—
		2	(0·0)	(5·0)	4·4*	—
		3	(0·0)	(5·6)	11·1*	—
0–44	45–84	1	(1·2)	3·7	30·0	45·0*
		2	(1·1)	(3·7)	12·2[1]	—
		3	(0·0)	(8·8)	13·3[1]	—
45–84	0–44	1	2·6	5·0	17·5	19·6*
		2	(0·0)	(1·5)	9·3	14·3*
		3	(0·0)	(3·2)	12·5[1]	—
45–84	45–84	1	(0·3)	4·6	16·0	19·0*
		2	(0·0)	(2·0)	12·5	26·3*
		3	(0·0)	(2·3)	15·2	18·0*

* At the average age of cell (not extrapolated).

Table 8. *Numbers of sibs of probands with two other first-degree relatives affected*

(T, Total; A, affected.)

Onset groups of affected relatives*			Current age-group							
			0–24		25–44		45–64		65–84	
			A	T	A	T	A	T	A	T
1	1	1	0	9	0	9	1	7	0	1
1	1	2	2	10	0	7	0	5	0	0
1	2	2	0	69	0	66	13	53	13	27
2	2	2	0	161	5	157	22	153	13	68

* 1, Onset 0–44; 2, Onset > 44.

With three affected relatives the numbers of sibs of probands are even more limited. The actual numbers for first-degree relatives are given in Table 8. Empiric risks are only available for older relatives of late onset patients.

DISCUSSION

The initial objects of this analysis were to derive tables of empiric risks for use in clinical practice and genetic counselling, and to compare the empiric risks with theoretical risks derived from a multifactorial model of inheritance of liability to diabetes. Neither objective has been satisfactorily achieved, largely because of difficulties inherent in the data which could not be entirely resolved. Instead emphasis has been on describing different kinds of estimates of empiric risks that might be derived and examining their strengths and weaknesses. Some estimates of the empiric risks are clearly underestimates. Other estimates, which try to avoid or adjust for obvious biases, may themselves have subtle deficiencies. Despite the large amount of data available, it did not prove sufficient for all the analysis attempted. The extent of possible partitioning, by sex, treatment or onset-age class, was quite limited because of the low frequency of early-onset diabetes and many cells in the derived tables had small numbers of relatives. The

Table 9. *Probable ranges of empiric risks in relatives*

	Risk (%) of being affected by age			
	25	45	65	85
Population risk	0·2–0·3	0·5–0·9	1·8–3·8	1·8–9·2
Affected first-degree relative				
Onset age				
0–24	5–8	5–13	5–17	7–25
25–44	1–2	2–3	6–10	13–19
45–64	0·2–0·5	0·5–1·5	8–10	13–20
65–84	0·2–0·5	1·5–2·0	6–8	15–22
Affected second- (or third-) degree relative	Divide above risks by 2			
Two first-degree relatives affected				
Onset age				
0–44, 0–44	Multiply above risks by 2–4			
0–44, 45–84	Multiply above risks by 1·5–3			
45–84, 45–84	Multiply above risks by 1·5–2			
First- and second- (or third-) degree relative affected	Multiply above risks by 1·5–2			

ata were even more limited when dealing with families having two or more affected individuals nd further restrictions were imposed on the analyses.

Concern over the various empiric risk estimates has been shown to be more than just an aca-emic exercise and to be worth while in estimating the appropriate empiric risks. Thus the best stimates of the risks are greater, by a factor of 1·5–3, than the simple estimates of risks derived om living relatives. It was shown that the risks estimated for a specified family history will sually be too low for diseases with variable age at onset, for more relatives may become ffected with time (Table 4). The risks of becoming affected by a certain age for individuals ith *at least* the specified family history were about 1·3 times larger than for individuals with nly the specified family history. Estimation of empiric risks from only living relatives will also ive values which are too low (Table 5). This is due to the differential mortality of diabetics Table 2). Inclusion of dead relatives usually gave higher empiric risk estimates, but the dif-erent methods of inclusion lead to estimates with different values and biases. Moreover, inclu-ion of dead relatives only adjusts for differential mortality and not for changes in detection ates or in disease frequency which are probably also occurring over time. The empiric risk stimates that are probably the least biased are those derived from the diagonal cells of the ables of onset age by current age in relatives (Table 1). All individuals in the diagonal cells are xposed to current disease levels and detection rates, and their mortality can be taken into ccount. These risk estimates also tended to be the highest derived and can be taken as maxi-um risk estimates. They correspond most closely to the estimates of potential population revalence of Falconer *et al.* (1971).

A summary of the empiric risk estimates applicable to our population is given in Table 9. The lower values in each category are derived directly from living relatives (estimate 1) and are ertainly underestimates of the risks to relatives. The upper values are derived from recently iagnosed cases among relatives (estimate 8). These provide the best estimates of risk. They re about 1·5–3 times the lower values which measure the observed empiric risks. The best

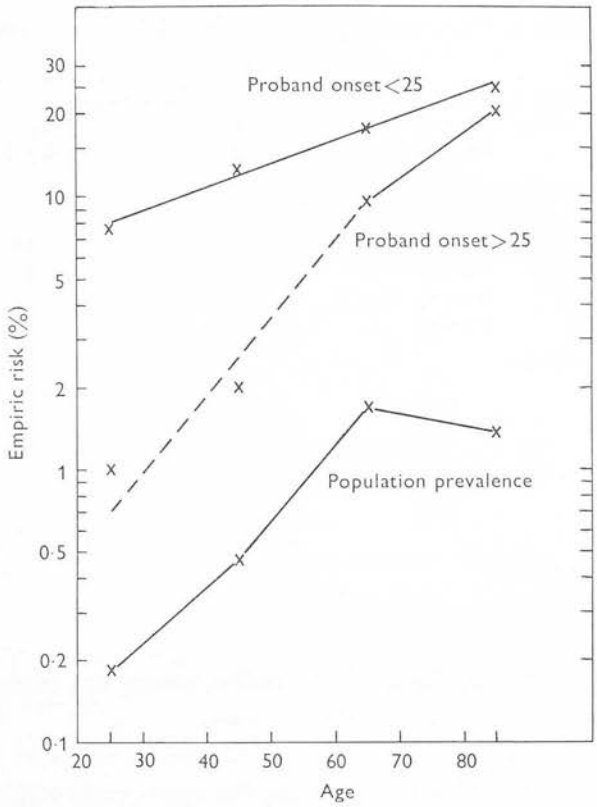

Fig. 3. Summary of estimated empiric risks to first-degree relatives of probands with onset (*a*) under 25, (*b*) over 25.

estimates are also given graphically in Fig. 3 in a more simplified form which may be useful to practitioners. For probands with onset over 25 the risks are similar and have been combined. The population empiric risk is given for comparison.

Summarizing the results for families with two or more affected individuals is more difficult because the small numbers available lead to rather heterogeneous results. Rather than give figures for the risk at each age, overall multiplication factors are presented to summarize the increased level of risks in these families.

There may be many other factors that affect risks to relatives and should be considered in counselling. For example, obesity in the proband and in the relatives might be taken into account (Baird, 1973). Another factor which might be considered is the severity of the diabetes in the proband and whether it is insulin-dependent. Patients whose diabetes is controlled by diet have a lower liability (Smith *et al.* 1972) and their relatives have a lower risk. Lestradet *et al.* (1972) found that the relatives of controls had the same frequency of non-insulin-dependent diabetes as relatives of insulin-dependent patients, but the latter had a much higher frequency of insulin-dependent relatives than did the controls. They went on to suggest that insulin-dependent and non-insulin-dependent diabetes may represent genetically independent types of the disease.

There are many studies in the literature on the prevalence of diabetes in relatives of diabetics but few take variable onset age into account and none seem to make allowance for differential

mortality in diabetics when assessing risks. Perhaps the largest set of data with age of relatives given is the Canadian study of Simpson (1969) on living relatives. The prevalence by age in living relatives was somewhat less than the corresponding empiric risks (estimate 1) derived here, as shown by the rather lower heritability estimates Simpson obtained. Steinberg (1955) has produced tables for genetic counselling in diabetes assuming an autosomal mode of inheritance. He gives the calculated proportion of relatives genetically liable to diabetes for different family histories. However, of the proportion who are deemed genetically liable, only some 30–40 % will actually manifest the disease. In general, with this small proportion of liable genotypes manifesting, the lifetime empiric risks estimated in this paper are higher than the risks calculated by Steinberg, except when both paternal and maternal relatives are affected.

There are several studies on the risks to monozygous (MZ) twins of diabetics and to children of diabetic couples. Simpson (1969) found the risks to children when both parents were diabetic three times as high as when only one parent was affected. Cooke *et al.* (1966) found 4·4 % of children of diabetic couples were affected but estimated that their lifetime risk would be about 15 %. Similarly, Kahn, Soeldner & Gleason (1969) showed that while 8·8 % of children of diabetic couples (aged 50–80) had overt diabetes, some 40–60 % had chemical diabetes as determined by abnormal glucose-tolerance tests. Thus the lifetime risks of diabetes in children of diabetic couples are likely to be high and in the range 20–50 %. The studies on MZ twins have been summarized by Tattersall & Pyke (1972) along with their own results. In studies where age at onset was taken into account, the concordance rates were about 50 % for early-onset diabetes (< 40), but were much higher, from 80 to 100 %, for late-onset diabetes. Though the methods of ascertainment favour concordant pairs, the results indicate high risks to MZ twins of diabetics. The high MZ concordance rates are not expected from a multifactorial mode of inheritance with intermedate heritability estimates, though a higher rate in the late-onset group is expected because of the higher frequency of late-onset disease. To resolve the high concordance rates, comparable rates for dizygous twins and unbiased methods of ascertainment of twins will be needed.

Early- and late-onset forms

One of the conclusions of the previous paper needs revision in the light of further results from the present analyses. In Smith *et al.* (1972) it was concluded that early-onset and late-onset diabetes represent different levels of liability to the same disease rather than being distinct diseases. This was because patients with early onset had relatives with late-onset disease in a much higher frequency than would be expected if two distinct diseases were involved. However, the analysis dealt only with *living* relatives. There was an anomaly of low genetic correlations for late-onset patients with early onset relatives compared with high genetic correlations for early-onset patients with late-onset relatives (Table 7, Smith *et al.* 1972). It was suggested that this anomaly was due largely to the effects of 'frequency reduction' (including differential mortality) and to a correlation between the current ages of patients and of their living relatives. To test whether the differential mortality of diabetics would account for the above anomaly, the analysis was repeated here using all cited relatives (living and dead). Since dead relatives were included, the actual population prevalence of living diabetics was no longer appropriate. But dead diabetics probands were not ascertained, so an appropriate estimate of the population frequency of all (living and dead) diabetics could not be derived. Instead an estimated popula-

tion frequency adjusted for differential mortality, as derived in the previous section (see Fig. 1) was used.

On re-analysis the heritability estimates were all somewhat lower than the estimates from living relatives, suggesting that the population frequency for all diabetics, described above, may be too high. The pattern of the genetic correlations is similar to that in the previous analysis and the anomaly between the two halves of the correlation matrix persists. Thus it can be concluded that the anomaly in the correlation matrix is not due to differential mortality of early-onset relatives of late-onset patients. To some extent the higher correlations for early-onset patients are to be expected since the frequency of the early-onset groups of relatives are added (in the cumulative model) into the other onset groups. However, this cumulation cannot account for the anomaly either, because the same anomaly exists when treating early-onset and late-onset diabetes separately (the separate model, Smith *et al.* 1972). Another result of a single distribution of liability is that the empiric risks should increase to the top right-hand corner of the risk tables. This occurs for the best estimate, (8) Table 5, but not for any of the other empiric risk estimates.

In general, the hypothesis that a single distribution of liability can summarize the observed data on diabetes in relatives now seems unlikely. Instead there seem to be different but overlapping distributions of liability for different onset age-groups. Indeed, there are likely to be many underlying genetic and environmental causes of diabetes, each with a characteristic onset age and risk distribution, and which our statistical methods are unable to resolve.

SUMMARY

Empiric risks of recurrence of diabetes in relatives of diabetics have been estimated from data on 25,635 relatives of 1367 living diabetics.

Several factors can affect estimates of the empiric risks and should be taken into account. These include variable age at onset, differential mortality of diabetics, changing detection rates, changes in the frequency of the disease and changes in family history over time. Various risk estimators are considered and the derived estimates are compared.

Differential mortality of diabetics increased with both onset age and duration of the disease, rising from 1–2 % per year for groups under 40 years to 3–5 % per year for groups over 40 years of age. Due to differential mortality, estimates of empiric risks from living relatives are too low, but they are simple to calculate and provide minimum risk figures. Inclusion of dead relatives leads to higher risk estimates, but the method of inclusion affects the risks obtained. The least-biased estimates are derived from the frequency of recently diagnosed cases in serial current age-groups and the risks estimated by cumulating the frequencies over age-groups. These are regarded as the best available estimates of risk and are summarized below:

	Risk (%) of diabetes by age:			
	25	45	65	85
In the population:				
Observed	0·2	0·5	1·7	1·4
Estimated	0·3	0·9	3·8	9·2
In first-degree relatives:				
Proband onset under 25	8	13	17	25
Proband onset over 25	(1)	(2)	9	21

The risks for second- and third-degree relatives were about half of those for first-degree relatives. If there are other affected individuals in the family, the risks increase further by a factor of 1·5–4 times, depending on the degree of relationship and age of onset of the other affected relative.

The conclusion (Smith *et al.* 1972) that early-onset and late-onset diabetes represent different levels of liability to the same disease, rather than being distinct diseases, now seems unlikely. On re-analysis of the data including dead relatives, it now seems more likely that there are different distributions of liability for different onset groups but they show a large degree of overlap.

We would like to thank Dr D. S. Falconer for helpful suggestions and discussions. We also gratefully acknowledge financial support from the British Diabetic Society and Pfizer Ltd.

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APPENDIX. AN ADJUSTMENT FOR CHANGING FAMILY HISTORY

The empiric risks for an individual with a specified family history can be estimated from data on all families with the specified history at each age. These are called the S risk estimates. However, the individual's family history may change with time, as other relatives become affected; then the risk would be higher than given by the S estimate. An upper bound for the risk estimate can be obtained by including families with *at least* the specified family history at each age. These risks are called the A estimates. The actual risk will lie between the A and S estimates, its position depending on the length of the period between the age at estimation and the age to which the estimate applies. A diagram of the situation is given in Fig. A 1, taking linear (or log. linear) risk curves for simplicity. Suppose an individual has a specified family history at age a_1, then the probability of being affected at age a_2 will be S_2, plus a proportion of the difference (A_2-S_2). This proportion will be $(a_2-a_1)/a_2$, which is equal to $(S_2-S_1)/S_2$ by symmetry. A better estimate of the risk at a_2, conditional on being unaffected at age a_1, is then

$$\frac{S_2+(A_2-S_2)\,(a_2-a_1)/a_2-S_1}{1-S_1},$$

APPENDIX (*cont.*)

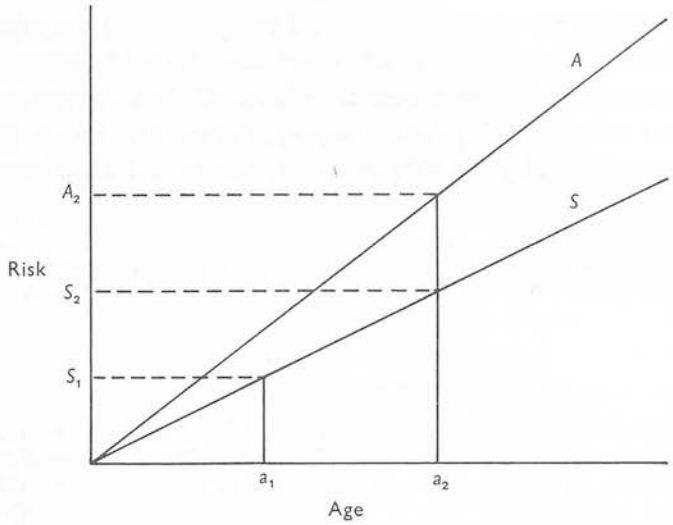

Fig. A 1. Diagram of risks estimated from families with a specified family history (S) and from families with *at least* the specified family history (A)

which reduces to

$$\frac{A_2\,(S_2-S_1)}{S_2\,(1-S_1)}.$$

If the risks increase logarithmically with age, then the A and S terms are replaced by their logarithms.

Rather than use point estimates in the above expression, the regressions b_A and b_S on age may be more reliable. Assuming that these regressions pass through the origin, if the risk at birth is zero, then the above expression reduces simply to

$$\frac{b_A}{b_S}\,\frac{S_2-S_1}{1-S_1},$$

the conditional S risk estimate times a constant multiplication factor. In the analyses of the A and S tables for pooled first-degree relatives the b_A/b_S multipliers were 1·33, 0·99, 1·57 and 1·13 for the four proband onset age-groups respectively.

Computer Programme to Estimate Recurrence Risks for Multifactorial Familial Disease

CHARLES SMITH

Summary

A computer programme to estimate recurrence risks for multifactorial genetic disease in affected families uses parameters on population prevalence and on heritability of liability of the condition and details of the family history. Information on affected and unaffected relatives (first-degree, second-degree, and third-degree) and on sex or age effects on prevalence and on heritability can all be accommodated by the programme.

Introduction

Many common familial diseases are not inherited in a simple Mendelian manner but may be the result of many genetic and environmental factors, so-called multifactorial inheritance. The recurrence risks for such diseases are not the simple Mendelian ratios and the best available estimates are the empiric risks—the observed frequency of the disease in relatives of affected patients. In practice, however, these risks may vary with the sex, severity, and age of onset in affected individuals and with the number of affected members in the family concerned. New methods of estimating recurrence risks for multifactorial conditions have been developed,[1 2] and these can be used in genetic counselling to supplement empiric risks in complex situations. The objects of this paper are to describe a computer programme available for calculating recurrence risks and to demonstrate its use in genetic counselling problems.

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Scope

A wide range of possible situations can be covered by the programme. It can accommodate: (1) affected and unaffected relatives; (2) any family history, giving (*a*) accurate risks within sibships but (*b*) approximate risks with second-degree and third-degree relatives; (3) differences in prevalence and heritability for different sexes or different severity or age classes for the disease; and (4) risks to future children or risks to an individual conditional on his not being affected so far.

A further development of the programme may allow the use of information on continuous variables associated with a disease (such as blood glucose levels in diabetes or personality scores in schizophrenia) and so improve the accuracy of the risk estimate in a given family.

Requirements

The most important requirements in genetic counselling are an accurate diagnosis of the condition involved and a complete family history for the condition. To estimate recurrence risks for multifactorial familial disease the population prevalence of the condition and the heritability of liability[3] to the condition are also required. The heritability of liability is measured from the frequency of the condition in relatives of affected individuals. Any effects of sex, severity, or age on the frequency of the condition must be taken into account in measuring the heritability and estimating the recurrence risks.

Computer Programme

A computer programme, RISKMF (the programme is written in FORTRAN and is available from the department of human genetics, Western General Hospital, Edinburgh), can be used to estimate the recurrence risks. Full details of the multifactorial model and of the methods used in the programme for calculating the recurrence risks were given by Smith.[1] The computer input to the programme consists of four items: (1) identification details—for example, family name, date, disease name; (2) the number (NCLASS) of severity or age (SA) classes specified; (3) the prevalence (P) and heritability (H) parameters for the condition; and (4) a coded family history (see below). These input details are printed in tables by the computer for checking and for reference. The recurrence risks are then calculated and printed.

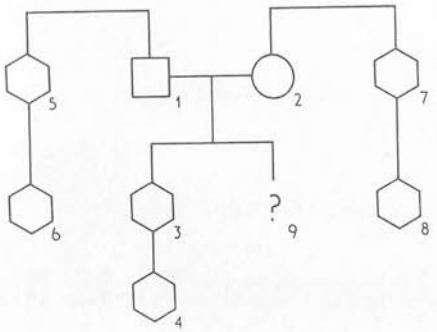

FIG. 1—Codes used for relatives (see text).

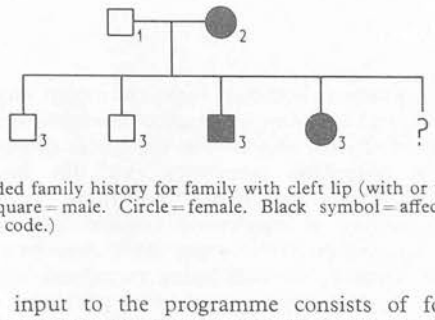

FIG. 2—Coded family history for family with cleft lip (with or without cleft palate). (Square = male. Circle = female. Black symbol = affected subject. See text for code.)

Coded Family History

A simplified form of the family pedigree is used, coded as shown in Fig. 1. The father is coded 1, and 5 and 6 code paternal second-degree and third-degree relatives respectively (and similarly for 2, 7, and 8 on the maternal side). Siblings are coded as 3 and siblings' children as 4. If the individual whose risk is sought is already born a code 9 is used. The form of the input details for each coded group in the pedigree is shown in the following examples.

INPUT DETAILS

(1) DISEASE CONDITION, FAMILY IDENTIFICATION, DATE, ETC. FORMAT (80A1)
FAMILY 0001 CLEFT LIP (WITH OR WITHOUT CLEFT PALATE) AUGUST 1971
(2) NUMBER OF SEVERITY-AGE (SA) CLASSES SPECIFIED FORMAT (I2)
1 = NCLASS
(3) PARAMETER MATRIX, PREVALENCE (P), HERITABILITY (H) FORMAT (6F6.4)

BOTH SEXES		MALES		FEMALES	
P	H	P	H	P	H
0·0010	0·7500	0·0013	0·7500	0·0007	0·7500

SA-CLASS
1
(4) INFORMATION MATRIX ON RELATIVES FORMAT (5I1)

CODE	NO.	SEX	CLASS	STATUS
1	1	1	1	0
2	1	2	1	1
3	2	1	1	0
3	1	1	1	1
3	1	2	1	1

OUTPUT DETAILS

RECURRENCE RISKS BY SEVERITY-AGE CLASS AND SEX

SEVERITY AGE CLASS	BOTH SEXES	MALE	FEMALE
1	0·134	0·155	0·109

FIG. 3—Input details and recurrence risks for the family (Fig. 2) with cleft lip (with or without cleft palate).

EXAMPLE 1

Consider the family in Fig. 2 with cleft lip (with or without cleft palate). The numbers refer to the codes in the simplified pedigree. The population prevalence of the condition is about 0·1% (0·13% in males and 0·07% in females) and the heritability is estimated as about 75% in both sexes.[4] The input details are listed in the sample of computer output in Fig. 3. The recurrence risks to future children in the sibship are then calculated and printed. The estimated risk in this family is 13·4%—15·5% for males and 10·9% for females.

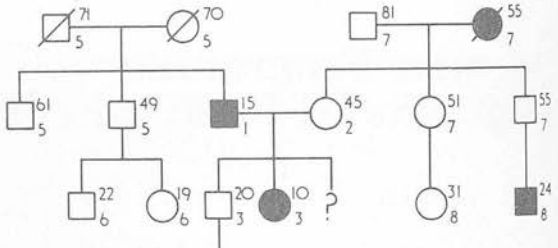

FIG. 4—Coded family history for family with diabetes mellitus. Key as for Fig. 2. Oblique line through symbol indicates subject dead. Superior number against white symbol indicates current age or age at death. Superior number against black symbol indicates age at onset. Inferior numbers refer to pedigree codes.

EXAMPLE 2

As a more complex example consider a family with diabetes mellitus. For diabetes there are sex effects on prevalence and age effects on heritability. Early-onset and late-onset cases are taken to belong to the same genetic condition.[5] In the family history given in Fig. 4 the age shown is the age at onset if the person is diabetic and the current age if the person is not diabetic. The pedigree codes are inserted as before. What is the risk of diabetes to future children at different stages in their lives?

The input details are given in the computer output, as shown in Fig. 5. Four severity-age classes have been specified corresponding to four onset-age classes (0-19 years, 20-39 years, 40-59 years, and 60-79 years), so NCLASS = 4. The varying prevalence and heritability parameters for different onset-age and sex classes, derived from Smith *et al.*,[5] are also shown. The severity-age class coded is the onset-age class if the relative is affected and the current-age class if the relative is not affected. The risks of diabetes to future children throughout their lives is given by the computer, as in Fig. 5. Similarly, for a person

INPUT DETAILS

(1) DISEASE CONDITION, FAMILY IDENTIFICATION, DATE, ETC.
FAMILY 0823 DIABETES MELLITUS
(2) NUMBER OF SEVERITY-AGE (SA) CLASSES SPECIFIED
4 = NCLASS
(3) PARAMETER MATRIX, PREVALENCE (P), HERITABILITY (H)

BOTH SEXES		MALES		FEMALES		
P	H	P	H	P	H	SA-CLASS
0·0005	0·7100	0·0005	0·7100	0·0004	0·7100	1
0·0019	0·6000	0·0021	0·6000	0·0016	0·6000	2
0·0075	0·5800	0·0079	0·5800	0·0071	0·5800	3
0·0192	0·5300	0·0192	0·5300	0·0192	0·5300	4

(4) INFORMATION MATRIX ON RELATIVES

CODE	NO.	SEX	CLASS	STATUS
1	1	1	1	1
2	1	2	3	0
3	1	1	2	0
3	1	2	1	1
4	1	2	1	0
5	2	1	4	0
5	1	2	4	0
5	1	1	3	0
6	1	1	2	0
6	1	2	1	0
7	1	1	4	0
7	1	2	3	1
7	1	2	3	0
7	1	1	3	0
8	1	2	2	0
8	1	1	2	1

OUTPUT DETAILS

RECURRENCE RISKS BY SEVERITY-AGE CLASS AND SEX

SEVERITY-AGE CLASS	BOTH SEXES	MALE	FEMALE
1	0·097	0·097	0·085
2	0·153	0·161	0·140
3	0·293	0·300	0·287
4	0·406	0·406	0·406

FIG. 5—Input details and recurrence risks for the family (Fig. 4) with diabetes mellitus.

who is not affected so far the risk of contracting diabetes can be estimated by the programme.

Discussion

This brief account should illustrate the scope of the RISKMF programme in evaluating recurrence risks for multifactorial conditions. In addition to estimating risks for individual families the programme can be used to provide theoretical recurrence risks in general situations or for comparisons with observed risks. For example, risks to children if both parents are affected (so-called dual matings), risks for sporadic cases, risks with two, three, or more affected children, and so on, can all be studied by the programme. The maximum risk with multifactorial inheritance, assuming a heritability close to 100%, can also be derived. Similarly the effects of varying the prevalence and heritability parameters or the number of SA classes or of including unaffected relatives or second-degree and third-degree relatives can all be studied empirically through the programme.

The programme can handle several families in sequence with the same or different diseases. At present data are fed to the computer by means of punch cards, but an interactive system with direct access to the computer by a teletype or other remote terminal is planned. Computing time per family is usually less than 30 seconds (I.B.M. 360 50). The programme, with documentation, is available on request from this department. Alternatively family histories, with the relevant prevalence and heritability parameters, may be submitted to the department for estimation of risk. Morton[6] has also developed a computer programme (COUNSEL) for estimating recurrence risks. His programme will allow the user to estimate risks by using several genetic models, including the multifactorial model.

The programme might also be used to prepare user tables of recurrence risks for a variety of family histories for a given condition, such as the specialty of a department, or for a particular geographical area. For example, the recurrence risks for spina bifida or anencephaly or both in a high-incidence area have been estimated for different numbers of affected relatives by using the data of Carter *et al.*[7] from South Wales (combined incidence 0·78%, heritability 64%). These are given in the Table and show how the risk increases as further affected relatives, including second-degree and third-degree relatives, are added. If there is no previous family history, however, the estimated risk is lower than the empiric risk.

Estimated Recurrence Risks for Spina Bifida or Anencephaly or Both

Family History	Estimated Risk (%)
One sib affected	5·5
Parent and sib affected / Two sibs affected	13·0
Three sibs affected	20·6
One sib and a second-degree relative affected	9·2
One sib and a third-degree relative affected	7·3
One sib affected, no other family history	3·7

The use of these methods to estimate recurrence risks in practice may be queried on several grounds. In man it is always difficult to separate genetic and non-genetic effects, and these may be confounded in estimating heritability. This is less serious for risk estimation, however, since non-genetic effects may also be involved in risks to relatives. The multifactorial model is used to describe the observed frequencies of a condition in relatives, but the true mode of inheritance is usually not known. This may not be too critical in evaluating risks, for it has been shown[8 9] that the risks are similar for different modes of inheritance—unless strict Mendelian inheritance is involved. Another difficulty in practice may be the lack of adequate estimates of population prevalence and of heritability, but these should accrue in time.

Finally, the recurrence risks for multifactorial conditions are usually not high unless the disease is common or there are several affected relatives in the family. Thus the methods described here may be of most value (1) in common familial conditions or (2) if there are complicating sex or age effects or (3) if there is a complex family history or (4) if there are poor empiric estimates of risk. Moreover, they provide a standard system and a rationale for estimating recurrence risks where none have been available previously. Thus they may help to provide better information for genetic counselling, for the identification of high-risk groups, for the indication for antenatal diagnosis, and in general for the prevention and treatment of familial disease.

I would like to thank Miss Susan Holloway for writing the programme for RISKMF, and my colleagues for helpful discussions.

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Equilibrium Frequencies in X-linked Recessive Disease

SUSAN M. HOLLOWAY[1] AND CHARLES SMITH[1]

Haldane's [1] formula for the equilibrium frequency of rare X-linked recessive diseases maintained by mutation can be extended to cover a wide variety of situations in genetic counseling, antenatal diagnosis, and eugenic consequences of different medical practices. Some of these have been considered already [2–4] but the studies have dealt with the effects of changing one factor at a time. In this paper, formulas are developed so that the net effect of any combined set of factors can be considered, in order to study the balance among different factors and their combined equilibria. The initial sections of the paper introduce the form of the procedure for simple cases; then the methods are generalized to take into account several variables concurrently. Finally, the use of the formulas is illustrated and discussed.

SIMPLE EQUILIBRIA

To introduce the methods and notation used (see Appendix), simple cases dealing with survival rates of affected males and reproductive practices of affected males and carrier females are considered. Let M and F be the equilibrium frequencies at birth of affected males and carrier females, respectively. Let the relative reproductive fitness (number of offspring born relative to the number of offspring born from normal individuals) of affected males and of carrier females be m and f, respectively. Note that this deals with the actual or achieved fertility, rather than with the potential fertility, genetic or otherwise.

Affected males are either the result of a new mutation or are the offspring of carrier females (half of whose sons are affected). Then, if μ is the mutation rate per gamete,

$$M = \mu + Ff/2. \tag{1}$$

Similarly, carrier females can arise by a new mutation (in either gamete), from carrier mothers (half their daughters are carriers), or from affected males (all daughters are carriers), so

$$F = 2\mu + Ff/2 + Mm. \tag{2}$$

The equilibrium frequencies can then be found, in terms of the mutation rate (μ), by substituting equation (1) in (2) and solving for F, giving

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$$F = \frac{\mu(2 + m)}{[1 - (f/2)(1 + m)]}, \tag{3}$$

and similarly for M.

These formulas can deal with changes in the fitness of affected males and carrier females as a result of genetic counseling or through improved treatment or survival of affected males. For example, if the fitness of affected males became 0.5 and that of carrier females was 0.8, then from equations (1) and (3) the equilibrium frequencies of affected males and carrier females would be 3.5 μ and 6.3 μ, respectively.

The formulas can be extended to deal with different mutation rates in males (μ_m) and females (μ_f). The contribution of mutation to M is μ_f and to F is ($\mu_m + \mu_f$). The solution for F then becomes $[\mu_m + \mu_f(1 + m)]/[1 - (f/2)(1 + m)]$, and similarly for M.

COMPLEX EQUILIBRIA

In practice, many other factors are likely to affect the net reproductive fitness of affected males and carrier females, so that the equilibrium frequency will usually be a complex function of several factors. Each of these will first be considered separately. Then the joint effect of the different factors will be considered, and general expressions from which the complex equilibria can be calculated will be derived.

Stage of Detection

If there is a previous family history of a disease or if carrier tests are available, carriers may be detected before any affected offspring are born. Following Fraser [2], this will be called prospective detection. However, most carriers of X-linked conditions will be detected only after the birth (or diagnosis) of an affected son; that is, detection is retrospective. Note that a proportion of carrier females will remain undetected since they have no affected offspring.

Among all carriers not detected prospectively, the proportion of cases born (or preventable) after the first case can be derived as follows. With family size n, an average of $n/4$ affected sons is expected. In a proportion $(3/4)^n$ of families of carrier females, there will be no affected sons. In the remainder $[1 - (3/4)^n]$, there will be at least one affected son, the first case in the family. Thus, the proportion of first cases among all cases in families of size n from carrier females is

$$z_n = [1 - (3/4)^n]/(n/4), \tag{4}$$

as shown by Fraser [5]. Table 1 illustrates this result for families of size three. The proportion of first cases among all affected is 37/48, which is equal to z_n for $n = 3$. The proportion of cases born after the first case is, of course, $(1 - z_n)$.

Since z_n is dependent on family size (n), the distribution of family size in the population must be taken into account. Fraser [5] has evaluated the weighted mean value ($\bar{z}$) for different distributions of family size. For example, for a Poisson

TABLE 1

PROPORTION OF FIRST CASES IN FAMILIES OF SIZE THREE

Family Order 1-2-3	Frequency (× 64)	No. First Cases	No. Affected	No. Normal Born before First Case	Total Normal Born
*NNN**	27	0	0	3	3
NNA	9	1	1	2	2
NAN	9	1	1	1	2
ANN	9	1	1	0	2
NAA	3	1	2	1	1
ANA	3	1	2	0	1
AAN	3	1	2	0	1
AAA	1	1	3	0	0
Total	64	37	48	111	144

* N = normal; A = affected.

distribution with mean family sizes of two and three, the proportions of first cases among all cases are 79% and 70%, respectively. With the negative binomial, the other distribution commonly used to describe distribution of family size, the figures are somewhat higher [5].

It can be shown that $\bar{z}$ also measures the proportion of normal individuals born before the first case. For example, in table 1 this proportion is 111/144. The quantity $\bar{z}$ also gives the average fitness of carrier females if they have no further children after the first case in their family.

Reproductive Fitness

The relative fitness of carrier females will depend on their reproductive practices after detection. Some may terminate their family, others may have normal family size, and still others may compensate for the birth of affected children. A proportion of all carrier females in the population will not be detected, and these are assumed to have normal family size. This group is included implicitly in all the results derived below.

Carrier females who are detected prospectively may have no children and will have a zero fitness. Any who partially restrict their family after detection will have a fitness of less than one, while those who go on to have their normal family size will have a fitness of one. Those terminating their families after the birth of an affected child will have a mean fitness of z.

Some carrier females may compensate for the birth of a affected children so as to have the intended number n of normal children, so-called full reproductive compensation. The total number of children born will be $(a + n)$. The ratio $a/(a + n)$ will be equal to p, the segregation ratio, so $n = a(1 - p)/p$. The mean fitness for such carrier females is then $(a + n)/n$, which is equal to $1/(1 - p)$; this result holds for any family size.

Some carrier females may wish for the intended number of living children. If a

proportion d of affected children do not survive, the total number of children born will be $(n + ad)$. By repeating the above argument, the fitness of such carrier females can be shown to be $1/(1 - dp)$.

Selective Abortion

To deal with selective abortion, the class of offspring selectively aborted must be considered. Various classes of offspring could be selectively aborted: (1) affected males, (2) all males, or (3) affected males and carrier females. Consider the reproductive fitness f^* of carrier females detected prospectively, measured in terms of number of offspring conceived (omitting natural abortions). The observed fitness f, in terms of numbers born, is then

$$f = f^*(x_{NF} + x_{NM} + x_{CF} + x_{AM})/4, \tag{5}$$

where x_{NF}, x_{NM}, x_{CF}, and x_{AM} refer, respectively, to the proportions born of normal females, normal males, carrier females, and affected males conceived. Thus the value of f^* can be derived. Similarly for affected males, female offspring (all carriers) could be selectively aborted. The observed fitness m in terms of offspring born is then

$$m = m^*(2y_{NM} + 2y_{CF})/4, \tag{6}$$

where y_{NM} and y_{CF} are the proportions born of normal males and carrier females conceived.

If the family is detected retrospectively, a proportion z of offspring will be born before detection, as shown in the previous section. The observed fitness f of carrier females in terms of offspring born then becomes

$$f = z + (f^* - z)(x_{NF} + x_{NM} + x_{CF} + x_{AM})/4. \tag{7}$$

Combined Equilibria

All the factors considered above can now be combined into a single set of formulas covering a wide range of situations and can deal with the various factors either singly or in combination.

As discussed earlier, all carrier females are unlikely to adopt the same reproductive practices after detection. To deal with this, let the subscript i refer to the ith group of carrier females who make up a proportion P_i of all carrier females. Similarly, let the subscript j and P_j refer to a particular group of affected males. The procedure then is to calculate, for each group i, the fitness f^*_i in terms of conceptions (given the observed fitness f_i in terms of births) and to weight the values according to the proportion in the group. The equilibrium frequencies can then be written as for equations (1) and (2), namely,

$$M = \mu + \frac{F}{2} \sum_i P_i[z_i + (f^*_i - z_i)x_{AM_i}]; \tag{8}$$

$$F = 2\mu + \frac{F}{2} \sum_i P_i[z_i + (f^*_i - z_i)x_{CF_i}] + M \sum_j P_j m_j y_{CF_j}. \tag{9}$$

By substituting in these formulas, the equilibrium frequencies can be easily derived. If there is no selective abortion, then $f^*_i = f_i$, and all x and $y = 1$. The formulas can be extended to deal with different mutation rates in males and females as before.

Application

To illustrate an application of the previous sections, consider a rather complex case—deriving the equilibrium frequency for an X-linked condition, say hemophilia. Affected males now tend to survive longer and may have more offspring than previously. Genetic counseling is available, and carrier tests and accurate diagnosis can be made. Selective abortion of males from carrier females and of daughters of affected males is also possible and may be used in a proportion of families.

Details of an example are given in tables 2 and 3. Among affected males, suppose 10% do not survive to reproduction, a further 20% have no offspring, and 60% have normal fitness. Suppose the final 10% of the affected males opt for selective abortion of their female offspring, half with no reproductive compensation and half with full reproductive compensation. However, since affected males do not pass X-linked genes to their sons and, using selective abortion, have no daughters, their actual fitness in this case need not be considered.

Among carrier females, those detected prospectively and those detected retrospectively must be treated separately (table 3). For prospective detection the details are similar to those for affected males. If carrier females terminate their family retrospectively, their average fitness ($\bar{z}$) will be about 70%–80%, as discussed earlier. If they use selective abortion of males but have the normal number of pregnancies, the relative fitness for conceptions (f^*) will be 1.0, and for offspring born (f) it will be 0.88. With selective abortion of males and normal family size, the fitness for numbers born (f) will be 1.0. The fitness for numbers conceived (f^*) is then given by $f = 1.0 = 0.75 + (f^* - 0.75)(1 + 1 + 0 + 0)/4$, so that f^* is 1.25. With selective abortion of males and a full family (n) of unaffected

TABLE 2

POSSIBLE REPRODUCTIVE PRACTICES FOR AFFECTED MALES SHOWING PROPORTION AND FITNESS FOR EACH TYPE

AFFECTED MALES	PROPORTION (P_j)	RELATIVE FITNESS	
		No. Born (m_j)	No. Conceived (m^*_j)
Not surviving	0.10	0	0
No offspring	0.20	0	0
Normal family size	0.60	1.0	1.0
Selective abortion of female offspring (n offspring conceived)	0.05	0.5	1.0
Selective abortion of female offspring (n offspring born)	0.05	1.0	2.0

TABLE 3

POSSIBLE REPRODUCTIVE PRACTICES FOR CARRIER FEMALES SHOWING PROPORTION AND FITNESS FOR EACH TYPE

A. DETECTION

	DETECTION OF CARRIER FEMALES	
	Prospective	Retrospective
Proportion	0.20	0.80
Proportion of offspring born before detection ($\bar{z}$)	0.0	0.75

B. REPRODUCTIVE PRACTICE

REPRODUCTIVE PRACTICE AFTER DETECTION	PROSPECTIVE PROPORTIONS (P_i)	FITNESS No. Born (f_i)	FITNESS No. Conceived (f^*_i)	RETROSPECTIVE PROPORTIONS (P_i)	FITNESS No. Born (f_i)	FITNESS No. Conceived (f^*_i)
No further offspring	0.30	0	0	0.40	0.75	0.75
Normal family size (n offspring born)	0.10	1.0	1.0	0.10	1.0	1.0
Selective abortion of males (n offspring conceived)	0.40	0.5	1.0	0.25	0.88	1.0
Selective abortion of males (n offspring born)	0.10	1.0	2.0	0.10	1.0	1.25
Selective abortion of males (n unaffected offspring born)	0.10	1.0	2.0	0.15	1.19	1.63

children, the relative fitness for offspring born (f) is equal to $1 + z/4$, since one-fourth of the children at detection will be affected, and the relative fitness for offspring conceived (f^*) is 1.63.

The values in tables 2 and 3 can be substituted directly in equations (8) and (9) to derive the equilibrium frequencies. These were found to be 3.7 μ for males and 8.4 μ for females. A computer program was written to derive the equilibrium frequencies for any set of variables studied and is available on request.

Relative Importance of Factors

One reason for trying to combine various factors affecting an equilibrium was to study their relative effects and to see where opposing forces would balance. A large variety of comparisons could be made using the above procedures, but only a few cases of special interest are considered here.

In the absence of selective abortion, the critical factor in determining the equilibria is the average fitness of carrier females, and similarly the average fitness of affected males. Thus, the combined effects of any group of fitnesses can be simply

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summarized by taking the average fitness for the group and substituting in equation (3) to get the equilibrium frequency.

With selective abortion, the type of offspring born, as well as their number, must be considered. So the average fitness does not summarize the effects of the various factors, and the full procedure as summarized by equations (7), (8), and (9) must be used. The effects of selective abortion with full reproductive compensation are of special interest, for these could theoretically give rise to a continuous increase in frequency with time. However, this is unlikely in practice, for there are other factors with balancing effects. The effects of a proportion of carriers having no children after detection are considered in figure 1. As this proportion

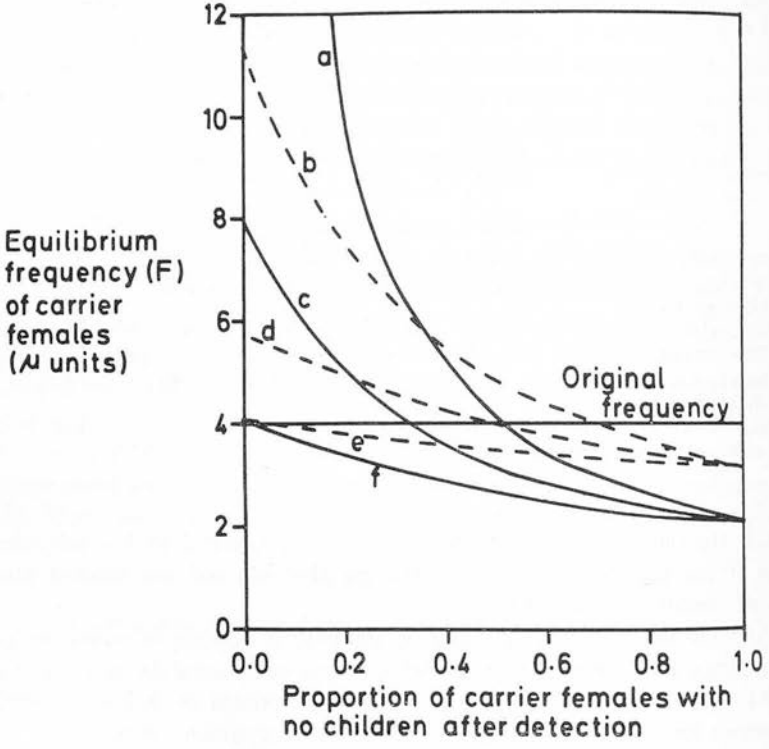

FIG. 1.—Equilibria from selective abortion of all males from carrier females following detection. (Affected males do not reproduce.) *Solid line* = prospective detection; *broken line* = retrospective detection; ($z = 0.7$).

increases the equilibrium frequency in each case falls. Case *a* shows the extreme situation with prospective detection and full reproductive compensation. If only a small proportion of detected carriers have no children, the frequency will not rise continuously but will reach a new, though elevated, equilibrium value.

With retrospective detection and full reproductive compensation (case *b*), much lower equilibrium frequencies are expected. However, a reduction in the number

of births from detected carriers will be expected in practice, since with selective abortion of males, two pregnancies are required on average for each female born. If carrier females have only their intended number of pregnancies, the equilibrium frequencies will be unchanged, or decreased if some carriers have no children after detection (cases *e* and *f*). The two other cases (fig. 1, *c* and *d*) represent intermediate situations. Case *d* refers to retrospective prevention where the intended number of offspring, including the affected proband, is produced. Case *c* represents prospective prevention where half the carriers practice full reproductive compensation and the other half have only their intended number of pregnancies. These result in only moderate increases in frequency above the original equilibrium value.

DISCUSSION

The equilibrium frequencies for X-linked diseases depend on many factors associated with survival and with reproductive practice of affected and carrier individuals. Several workers, but especially Fraser [2], have discussed the effects of changes in single factors acting in isolation, that is, assuming that other factors remain unchanged. The estimated changes in frequency have been very relevant in setting upper limits for the effect of each factor. In practice, several factors are likely to change concurrently, so that to estimate new equilibrium levels more accurately, methods to take the various factors into account are required. The methods outlined here allow combination of any set of factors in order to study and assess their combined equilibrium.

Though the theoretical derivation of equilibria is clear, their determination in practice may be more difficult because the statistics required may be difficult to estimate reliably and will vary over time and place. If the disease is rare, the numbers in various reproductive groups may be small and variable and thus contribute to unreliable estimates. The distributions of intended and completed family size will only be known in retrospect, after reproduction has ceased and may also vary with time. Similarly, the fitness of an individual cannot be measured until the end of reproductive life. These derivations also assume that the disease is caused by a single genetic entity. Both genetic heterogeneity and the existence of phenocopies are factors that would affect the equilibrium values for the frequency of the disease.

With X-linked conditions the approach to new equilibrium levels is reasonably rapid [6], reaching halfway to the new equilibrium in 3–6 generations, compared with hundreds of generations for autosomal recessive conditions. However, it is likely that survival, reproduction, detection, selective abortion, and other factors will change with time and will differ between countries, social groups, and so on. Thus, the equilibria are unlikely to be constant but will continue to vary over time and place.

SUMMARY

Formulas are developed to calculate the equilibrium frequency of X-linked diseases in complex situations. These include the combined effects of survival of

affected individuals, variable reproductive performance of affected males and carrier females, variable stages of detection, and selective abortion. The net effect of any combined set of factors on the equilibrium frequency of the disease can thus be studied.

APPENDIX

Symbols

NF, NM, CF, AM = normal females, normal males, carrier females, affected males
F = equilibrium frequency of CF born
M = equilibrium frequency of AM born
p = segregation ratio
μ = mutation rate per gamete per generation
n = family size
a = average number of AM
z = proportion of offspring born before detection of the family

Parameters Varying with Reproductive Class

P_i = proportion of CF in class (i)
P_j = proportion of AM in class (j)
f_i = relative fitness of CF in class (i) in terms of offspring born
m_j = relative fitness of AM in class (j) in terms of offspring born
f^*_i = relative fitness of CF in class (i) in terms of offspring conceived
m^*_j = relative fitness of AM in class (j) in terms of offspring conceived
x_{NF_i} = proportion of NF born among those conceived by CF in class (i) after detection
y_{NM_j} = proportion of NM born among those conceived of AM in class (j)

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response such as G.V.H. This does not, however, exclude the possibility that patients who may develop G.V.H. are also prone to skin infections and T.E.N.

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ANENCEPHALY, SPINA BIFIDA, AND POTATO BLIGHT IN THE EDINBURGH AREA

SIR,—Renwick [1] presented evidence of an association between the frequency of anencephaly and spina bifida on the one hand and the severity of blight in the potato crop in the previous year on the other. Later,[2] he presented further data showing very good matching between the number of live births with spina bifida in the West of Scotland during the 6-year period 1952–57 and blight scores in the area *two* years previously. More recently,[3] he found a high correlation ($r=0{\cdot}87$) between the adjusted annual frequency of anencephaly in the whole of England and Wales from 1961 to 1968 and the percentage of visibly blighted tubers at harvest in the previous year. We present a similar set of data for the Edinburgh area, dealing with dates of conception rather than with dates of birth and for a 17-year period from 1954 to 1971.

Blight scores for the potato crop in the East and South-East of Scotland were derived from assessments of progress of the disease on potato haulm (see accompanying table). A severe blight year (rated 2) was defined as one where there was at least 75% haulm death in unsprayed crops before the end of August.[4] Years when blight was clearly of little importance on haulm and in tubers were rated 0, and intermediate years were rated 1. These assessments were supplemented by data on experimental plots in commercial crops at several locations during the years 1959–68.[5] Independent assessments of tuber blight for crops in Scotland made just before harvest were obtained from the Potato Marketing Board. There was good agreement between the two sets of blight assessments ($r=0{\cdot}68$). There was no apparent trend over years in the percentage of blighted tubers at harvest ($r=-0{\cdot}06$).

Practically all the potatoes consumed in the Edinburgh area from August to April are produced locally. The old potato crop continues to be eaten through May and early June but is gradually replaced first by imports in May and then by early crops from other parts of the U.K. The interval from July in one year (N) to June in the next year (N+1) has been taken as the period when the crop corresponding to the blight scores for year N is consumed and when conceptions relevant to the blight scores occur.

Records on all stillbirths and deaths under 28 days with anencephaly or spina bifida were available for the period 1954–71 inclusive from the birth registers of the Simpson Memorial Maternity Pavilion in Edinburgh, the largest maternity hospital in the area. Details on the reported month of conception were available. The number of cases conceived in the period July to June in each yearly interval was then counted and adjusted to the mean number of 5000 births per year. The results are given in the table. There was a highly significant downward trend ($P<0{\cdot}01$) over years in the number of cases. To express the numbers relative to their contemporary mean, they are also given as deviations from the linear regression of numbers on years. The deviations among years were then no longer significantly heterogeneous ($P<0{\cdot}20$).

In the table, years with high blight scores showed no tendency to have a high number of cases. Although it was possible to match certain parts of the data, over the whole 17-year period there was no association between the blight assessments and the number of cases ($r=-0{\cdot}08$). Since the numbers were small in any one year, the data were grouped by blight score, combining scores 0 and 1. A Kruskal-Wallis analysis of rank test was performed, but the difference in the sums of the ranks of the two classes was trivial. The difference between the means of the deviations in the two classes (2 minus [0+1]) was $0{\cdot}9\pm3{\cdot}3$ cases. Our data would be large enough to detect as significant ($P<0{\cdot}05$) differences in the frequency of affected cases of about 25% between blight and non-blight years. This is of the order of the differences found by Renwick in Scottish data.[4] The data did show highly significant monthly differences in the number of cases; conceptions of cases were markedly elevated in May ($\times1{\cdot}57$) and August ($\times1{\cdot}46$) and were low in February ($\times0{\cdot}73$).

ANNUAL ASSESSMENTS OF BLIGHT IN POTATO HAULM AND TUBERS, AND THE NUMBER OF CASES OF ANENCEPHALY AND SPINA BIFIDA CONCEIVED IN THE SAME CROP YEAR (SEE TEXT)

Crop year (N)	Haulm blight score	Tuber blight (%)	No. of cases (adjusted)	Deviations from the linear trend
1954	1	1·04	23	−15
1955	0	0·28	46	9
1956	1	1·38	23	−12
1957	2	1·33	36	2
1958	2	1·74	31	− 2
1959	0	0·47	40	8
1960	2	1·32	32	1
1961	1	0·94	38	8
1962	1	0·92	24	− 5
1963	2	3·98	30	2
1964	1	1·03	24	− 2
1965	2	1·49	28	3
1966	2	1·42	15	− 9
1967	1	0·44	22	− 1
1968	2	1·41	20	− 2
1969	0	0·47	19	− 2
1970	0	0·41	16	− 4

In summary these data from the Edinburgh area, dealing with blight in the potato crop and conceptions in the same crop year, do not support the reported association between the severity of potato blight and the frequency of anencephaly and spina bifida.

We thank Dr J. C. H. Dunlop and his records staff at the Simpson Memorial Maternity Pavilion and the Potato Marketing Board for use of their collected records.

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ANENCEPHALY AND POTATOES IN CHILE

SIR,—I am very interested in Dr Renwick's hypothesis that blighted potatoes are related to the increase of anencephaly in Chile.[6–8] I am reporting preliminary data in order to clarify the situation. During the decade before the introduction of potato-blight-resistant potatoes (1940–49) the average potato yield was 9 metric tons per hectare and the average production per head 80 kg. This figure fell to 60 kg. in the worst blight year in 1951, but yield was not affected. The following figures show that these averages have not varied during the past decade. Unfortunately we

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Concordance in Twins: Methods and Interpretation

CHARLES SMITH[1]

INTRODUCTION

Monozygous (MZ) and dizygous (DZ) twins provide a unique and valuable set of material for the study of inheritance of traits and diseases in man. Yet the twin method and twin results are often not given the weight or attention they deserve. This is partly because of the variety of methods used and the different genetic interpretations made, which are sometimes inappropriate. There is need for a simple account of the twin method for clinical geneticists and other users who lack statistical expertise. The object of this paper is to present a simple, standard procedure for collecting, analyzing, and interpreting twin concordance data. The effects of factors such as common familial environment are taken into account, and other methods of analysis and interpretation are considered. Several workers [1–3] have already dealt with particular aspects of twin concordance, and the relevant results, along with some new results, are presented here.

METHODS

Proband Concordance Rate

The methods in this paper deal specifically with discontinuous traits such as disease, where individuals are classed as 1 if they have the trait and as 0 if they do not. Consider first all N pairs of twins of one kind (MZ or DZ) in the population and assume that all individuals are correctly classed as 1 or 0. The numbers of the four types of twin pairs (11, 10, 01, and 00) are given by n_{11}, n_{10}, n_{01}, and n_{00} as in the 2×2 table in table 1, and the proportions are $P_{11} + P_{10} + P_{01} + P_{00} = 1$. The frequency ($P$) of the trait can be measured in the population or, alternatively, in the twins themselves (though far less precisely) as $P = (2n_{11} + n_{10} + n_{01})/2N = (2P_{11} + P_{10} + P_{01})/2 = P_{11} + P_{10}$.

If we deal with twin pairs, it is obvious that pairs of type 00 will not be ascertained for the trait. Similarly, those of type 11 may have a greater chance of being ascertained and being in the sample observed than 01 or 10 pairs. The complications introduced by these ascertainment problems can be avoided by dealing with the individual rather than with the twin pair. The simplest and most appropriate measure of concordance is the *proband* concordance rate, the proportion of cotwins with the trait for individuals independently ascertained. Each twin pair is then

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TABLE 1

NUMBERS (n) AND PROPORTIONS (P) OF ALL TWIN PAIRS IN THE POPULATION

TWIN CLASS	COTWIN CLASS 1	COTWIN CLASS 0	TOTAL
1	n_{11} (P_{11})	n_{10} (P_{10})	$n_{11}+n_{10}$ (P)
0	n_{01} (P_{01})	n_{00} (P_{00})	$n_{01}+n_{00}$ ($1-P$)
Total	$n_{11}+n_{01}$ (P)	$n_{10}+n_{00}$ ($1-P$)	N (1)

NOTE.—Individuals classified as 1 if they have the trait and as 0 if they do not.

counted once for each member independently ascertained. This is equivalent to the Weinberg proband method [4] in segregation analysis, and the estimate is independent of the ascertainment frequency (see below). The proband concordance rate (P_R) is then

$$P_R = \frac{2n_{11}}{2n_{11}+n_{10}+n_{01}} = \frac{2P_{11}}{2P_{11}+P_{10}+P_{01}} = \frac{P_{11}}{P}. \qquad (1)$$

Interpretation

For Mendelian traits, the proband concordance rate gives an estimate of the segregation ratio. The expected values are, of course, 1 in MZ twins and ½ for dominant and ¼ for recessive traits in DZ twins. However, if penetrance is not complete or there are sporadic cases, then the observed rate will be less than expected. The ratio of observed to expected gives a guide to these effects, but full segregation analysis, treating twin pairs as families of size two, should be used to estimate the degree of penetrance, proportion of sporadic cases, and ascertainment frequency.

Interpretation of the proband concordance rate for traits not inherited in a simple Mendelian manner is arbitrary. However, a useful and robust method is to assume that the trait has an underlying continuous distribution of liability. Individuals then have the trait if their liability exceeds a certain threshold value on the distribution scale [5]. If the underlying distribution is continuous, it can be transformed (conceptually) to normality by an appropriate transformation of scale. The concordance rate can then be interpreted as a correlation coefficient in liability between relatives, corresponding to the correlation between relatives for a continuous trait. To estimate the correlation coefficient, both the population frequency of the trait and the proband concordance rate are required, as shown in table 2. For example, if the population frequency (P) is 0.5% and the proband concordance rate

TABLE 2

PROBAND CONCORDANCE RATE (FREQUENCY PER 1,000 COTWINS), GIVEN THE POPULATION FREQUENCY AND CORRELATION IN LIABILITY BETWEEN TWINS

	POPULATION FREQUENCY (%)									
CORRELATION	0.01	0.05	0.1	0.5	1	5	10	20	50	80
.1	1	2	3	11	19	74	133	241	532	810
.2	2	4	7	21	34	105	172	284	564	821
.3	4	10	14	37	55	143	216	331	597	833
.4	9	20	28	62	86	188	266	381	631	845
.5	18	38	51	98	129	244	324	436	667	859
.6	36	70	90	151	187	310	390	496	705	874
.7	70	125	152	226	266	392	468	565	747	891
.8	138	221	255	336	376	495	563	645	795	911
.9	291	400	434	507	542	637	689	750	857	937
.95	459	558	585	642	670	742	779	823	899	956
.99	736	789	802	841	845	885	898	922	957	981

(P_R) is 6.2%, the correlation between twins is estimated as .4. Other values can be found by interpolation using table 2, from published tables for the tetrachoric correlation, or from published graphs [6, 7].

A very simple approximate estimate of the correlation (r) in liability is given by

$$r = \frac{x - x_R}{a}, \tag{2a}$$

where a and x are the mean deviate and threshold value for individuals with the trait, and x_R is the difference between the threshold and the mean liability for relatives [8, 9]. However, this is an underestimate; an improved estimate is given by

$$r = \frac{x - x_R\sqrt{1 - (x^2 - x_R^2)(1 - x/a)}}{a + x_R^2(a - x)}. \tag{2b}$$

In the above example, when $P = 0.5\%$, $x = 2.576$ and $a = 2.892$; when $P = 6.2\%$, $x_R = 1.538$. Substituting in equation (2b), $r = .4$.

Standard Error

The standard error of the correlation in liability can be derived in several ways [5, 7, 9]. A simple approximate estimate can be derived as follows. In practice, the population frequency estimate will have a low variance, and so the variance of the correlation will depend largely on the number of affected cotwins in the sample. The variance is then given approximately [5] by

$$v = \left(\frac{1}{a^2}\right)\left(\frac{1}{a_R^2}\right)\left(\frac{1 - P_R}{A}\right) \tag{3}$$

where a and a_R are the mean deviates of individuals and of cotwins with the trait,

respectively. In this case, A should be taken as the number of twin pairs with both members affected. This avoids the effect on the variance of counting some pairs twice in calculating the proband concordance rate. An example will show how the formula is applied. Suppose that $P = 1\%$ and $P_R = 13\%$ from 100 independently ascertained MZ twins representing 96 twin pairs in all. From the normal distribution, $a = 2.665$, $a_R = 1.627$, $(1 - P_R) = .87$, and $A = 13 - (100 - 96) = 9$. From this set of data the estimate of the correlation and its standard error would be $.5 \pm .072$.

Genetic Interpretation

To interpret the correlations between twins in genetic terms, it is important that any nongenetic familial effects be eliminated. The best way to avoid these effects is to compare twins reared apart, but numbers are usually small and prenatal and perinatal effects remain. A more common method is to compare the correlations from MZ and from DZ twins. The correlations, as intraclass correlations, estimate the proportion of the total phenotypic variation (V) which is common to members of a twin pair. Thus

$$r_{MZ} = (V_A + V_D + V_C)/V = (V_G + V_C)/V \tag{4}$$

and

$$r_{DZ} = (\tfrac{1}{2}V_A + \tfrac{1}{4}V_D + V_C)/V, \tag{5}$$

where V_G is the total genetic variance, V_A is the additive genetic variance, V_D is the dominance genetic variance, and V_C is the variance due to nongenetic familial effects among twins [10]. Epistatic variance due to interactions among loci is ignored. If $V_C = 0$, then r_{MZ} gives a direct estimate of V_G/V, which is the coefficient of genetic determination (G), that proportion of the variation in liability among individuals in the population due to genetic effects. If V_C and V_D are small, $2r_{DZ}$ can be used to estimate the heritability (h^2) of liability, that proportion of variation in liability due to genetic effects which are directly transmittable to offspring. In practice, however, the values of these other variances are not known, and these estimates of G and h^2 may be seriously biased. Nongenetic familial effects can be eliminated, assuming they are the same for MZ and DZ pairs, by the expression

$$2(r_{MZ} - r_{DZ}) = (V_A + \tfrac{3}{2}V_D)/V. \tag{6}$$

This will overestimate the coefficient of genetic determination if V_D (or epistatic variance) is important and will approach the heritability if V_D is small. Since nongenetic familial effects usually give most concern in making genetic interpretations from twin studies, the above expression is the best form for interpreting concordance rates in twins. However, because it is twice the difference of two independent correlations, its standard error will be about $2\sqrt{2}$ times the standard error of the individual correlations. Thus a larger set of twin data will be needed to obtain precise estimates of the genetic determination of the trait.

COMPLICATIONS IN PRACTICE

After the simple outline of the proband concordance rate and its genetic interpretation, now consider some of the complicating factors that often arise in practice.

Sex Effects

Any sex difference in frequency of the trait must be taken into account in estimating the correlation between twins. This is done by ensuring that the appropriate population frequencies are used to (1) represent affected individuals and (2) represent the relatives considered. For example, in dealing with female cotwins of male individuals, the x in expression (2a) would refer to the frequency among females in the population and the a to the frequency in males. Suppose the frequency is 0.5% in males ($x_M = 2.576$, $a_M = 2.892$) and 1.0% in females ($x_F = 2.326$, $a_F = 2.665$), and the proband concordance rate for female cotwins of male individuals is 10% ($x_R = 1.282$); the correlation, using equation (2a), is then $(2.326 - 1.282)/2.892 = .36$. In expression (2b), the first two x have to be replaced by x_F, giving $r = .39$. This adjustment for differences in frequency in the sexes corresponds to Falconer's method 3 [5] and to Smith's formula [7, p. 87].

In MZ twins there will then be two estimates (r_{MM} and r_{FF}) and in DZ twins four estimates ($r_{MM}, r_{MF}, r_{FM}, r_{FF}$), where the first subscript refers to the individual and the second to the cotwin. Any significant difference among these should be examined in more detail. Otherwise the estimates can be pooled, weighting them in proportion to the inverse of their variances. The genetic interpretation of r_{MZ} and r_{DZ} can then proceed as before.

Age of Onset and Severity

If there is variable age of onset or variable severity, the analyses can become quite complex. The simplest procedure is to consider the frequencies among individuals and among cotwins at a certain age, including them in the analysis only if they manifested the trait at (or before) that age. The appropriate population frequency at that age would then be required. Analysis at different ages would then show the trend in the correlation with age.

A similar procedure could be adopted for degree of severity, including only individuals and their cotwins with a specified level of severity or worse. Here the correlation can be derived across levels of severity as well as within each level [9]. However, such estimates will not be independent.

Diagnosis and Ascertainment

In practice, not all individuals with the trait may be diagnosed, and among those diagnosed not all may be ascertained. In addition, different rates of diagnosis and of ascertainment may apply to cotwins after one member of the pair has been ascertained [11]. These factors can be taken into account easily by the proband concordance method and a general form of analysis derived.

Suppose only a proportion (c) of individuals with the trait in the population are diagnosed. A different rate of diagnosis (c') may apply to cotwins of ascertained individuals. Similarly, among those diagnosed, proportions of individuals (π) and of cotwins (π') may be ascertained. The situation is shown in table 3 in terms of individuals and their cotwins rather than twin pairs, in order to give the proband concordance rate. It is apparent from table 3 that several different estimates of

TABLE 3

PROPORTIONS OF INDIVIDUALS AND THEIR COTWINS WITH VARIABLE RATES OF DIAGNOSIS AND ASCERTAINMENT FOR INDIVIDUALS AND THEIR COTWINS

Trait	Twin			Cotwin			
				1			0
	Frequency			P			$1-P$
		Diagnosis		c'		$1-c'$	...
			Ascertainment	π'	$(1-\pi')$	...	...
1	P	c	π				
			$(1-\pi)$		n_{11} (P_{11})		n_{10} (P_{10})
		$1-c$	...				
0	$1-P$	...	...		n_{01} (P_{01})		n_{00} (P_{00})

population frequency and proband concordance rate can be derived depending on the rates of diagnosis and of ascertainment for individuals and their cotwins. These are summarized in table 4. For example, in case 6 the number of individuals ascertained is $2\pi cPN$, where N is the total number of pairs. From table 3, these individuals will have a total of $2\pi cP(n_{11}+n_{10})$ cotwins, and $2\pi cP(n_{11})$ $\pi'c'$ of these will also be diagnosed and ascertained with the trait. The proband concordance rate

TABLE 4

FREQUENCY IN COTWINS (PROBAND CONCORDANCE RATE) FOR DIFFERENT RATES OF DIAGNOSIS AND ASCERTAINMENT IN THE POPULATION AND AMONG COTWINS

Individuals	Population Frequency	Frequency in Cotwins: All with Trait	Those Diagnosed	Those Diagnosed and Ascertained
All with trait	P	P_R (1)	...	...
Those diagnosed	cP	P_R (2)	$c'P_R$ (3)	...
Those diagnosed and ascertained	πcP	P_R (4)	$c'P_R$ (5)	$\pi'c'P_R$ (6)
Appropriate population frequency for cotwins*	...	P	$c'P$	$\pi'c'P$

* Population frequency with which the frequency in twins should be compared.

is thus $\pi' c' n_{11}/(n_{11} + n_{10}) = \pi' c' P_R$, and similarly for the other cases in table 4. The other cases, of course, are particular examples of case 6 with one or more of the diagnoses or ascertainment rates equal to unity. An appropriate population frequency for comparison with the cotwins must be used (as already discussed for sex differences in frequency) and is also given in the table.

A variety of possible methods in the collection of data on twins can be covered by the results in table 4. For example, if the twin data are collected from records, then the same levels of diagnosis and of ascertainment will apply to individuals and their cotwins; that is, $c = c'$ and $\pi = \pi'$. If the cotwin is examined because its twin was ascertained, then the diagnosis rate may be higher than in the population, and all cotwins will be ascertained. Twin pairs from a twin register will have been ascertained for other purposes and not through the trait in question. But diagnosis may be incomplete and may differ in rate between the twin and cotwin, so that case 3 would be appropriate.

Population Frequency

To estimate the correlation between twins, the appropriate population frequency for the trait is required. Often this is not given, thus restricting interpretation of the results. Cavalli-Sforza and Bodmer [12] propose a method for estimating upper and lower limits for the coefficient of genetic determination from the MZ and DZ correlations. However, this method ignores nongenetic familial effects and requires other assumptions. A more satisfactory empirical procedure would be to determine a likely range of population frequency and estimate the correlations and coefficients of genetic determination at the upper and lower limits of the range of population frequency [13].

Correlation and Level of Ascertainment

The proband concordance rate avoids the problems of incomplete ascertainment. But the correlation estimates derived may be different at different levels of ascertainment. This is because both the population frequency and the proband concordance rate will be underestimated by incomplete ascertainment (although their ratio may be unchanged). Incomplete ascertainment is considered as an additional source of "error" variance by the liability model and so reduces the estimate of the correlation between twins. Thus for $P = 1\%$ and $P_R = 5.0\%$, $r = .28$, whereas if both frequencies are halved by incomplete ascertainment, $r = .23$.

The extent of the underestimation of the correlation for a range of correlations and population frequencies is shown in figure 1. These results were derived by reducing by the same proportion (.9, .5, or .1) the frequencies in twins and in cotwins for a given correlation and then reestimating the correlation at the reduced frequencies. The true correlations in liability are underestimated substantially at high population frequencies and if the diagnosis and ascertainment rates are low. This applies both to individual correlations and to the estimate $2(r_{MZ} - r_{DZ})$. Thus quite different estimates of the correlation in liability might be expected from data collected in different ways.

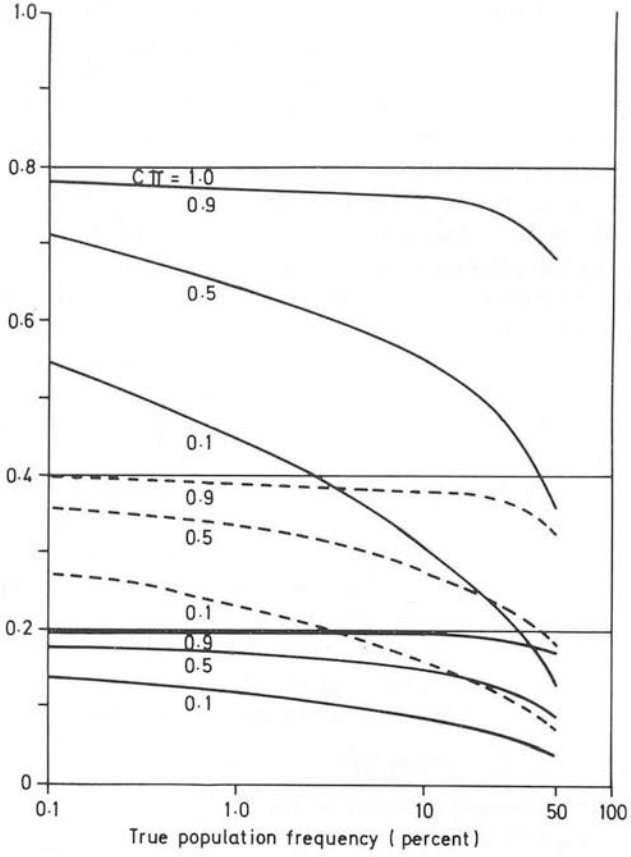

FIG. 1.—Graph showing effect of incomplete rates of diagnosis and of ascertainment at different population frequencies on the correlation in liability between twins.

The level of ascertainment (π) can be found in a way analogous to the proband concordance rate, namely as the proportion of affected cotwins who are themselves independently ascertained as probands. The observed population frequency and proband concordance rate can then be adjusted (by dividing by π) to the frequencies expected with complete ascertainment and the correlation in liability estimated.

MISAPPLICATIONS

The simple methods of estimation and interpretation of the proband concordance rate contrast with others which are still used in the human and medical genetic literature. In the next section consider, for completeness, some of the alternative measures of concordance. Because these cannot be interpreted simply as a segregation ratio or as a correlation in liability, their phenotypic and genetic interpretation is much more complex and their use should be discontinued.

The most common measure of twin concordance used in the past is the pairwise concordance rate (P_W), the proportion of concordant pairs among a set of ascertained twin pairs. This measure depends on the rates of diagnosis and ascertainment. If diagnosis and ascertainment are complete, P_W reduces to $P_R/(2 - P_R)$, so the two expressions of concordance can be derived from each other. If diagnosis and ascertainment are not complete, they must be taken into account. The pairwise concordance rate can be derived from table 3 and equals $P_{11}(2\pi'c' - \pi c)/[P_{11}(2 - \pi c) + P_{10} + P_{01}]$. This reduces to the expression given by Smith [3] if $\pi'c' = 1$ and to the previous expression if $\pi'c' = \pi c = 1$. If there is also single ascertainment (πc is very low), then the pairwise concordance rate approaches the proband concordance rate. Hrubec [11] uses another measure of concordance, the "casewise" concordance rate. This appears to be the above expression with the last two terms in the denominator divided by two. It does not seem to have any special properties of value but approaches the proband concordance rate when $\pi'c'$ and πc are close to one.

If ascertainment is not associated with the trait being studied, all types of twin pairs have an equal chance of being included in the analysis. Thus there is no ascertainment bias. This is often the case for twin panels assembled for a series of genetic studies. The proband (and pairwise) concordance rates apply as before. The overall or total concordance rate (P_T) may then be of interest; that is, the proportion that 11 and 00 concordant pairs are of all pairs so that $P_T = P_{11} + P_{00} = 1 - 2P(1 - P_R)$. It depends greatly on the population frequency, but may be used when the frequency of the trait in the population is intermediate.

Holzinger's Index of Heritability (H)

Holzinger [14] proposed an index of heritability (H) as $H = (V_{DZ} - V_{MZ})/V_{DZ} = (r_{MZ} - r_{DZ})/(1 - r_{DZ})$, where V_{MZ} and V_{DZ} refer to the variances *within* twin MZ and DZ pairs. A similar index, $H_C = (C_{MZ} - C_{DZ})/(1 - C_{DZ})$, was proposed to deal with concordance rates in MZ and DZ twins. These indices are still widely used in human genetics and related fields. However, they are arbitrary indices with no specific genetic interpretation, and they may not be comparable in different situations. Moreover, they give estimates of "heritability" which may be quite different from those commonly used in quantitative genetics, so they may be misleading and inappropriate.

The relation between the coefficient of genetic determination (G) and Holzinger's (H) is graphed in figure 2 for a range of correlations in MZ and DZ twins. The G and H values show only small areas of overlap, so the two estimates will often give quite different guides to the importance of genetic effects. For example, if $r_{MZ} = .5$ and $r_{DZ} = .1$, then $G = 0.8$ and $H = 0.4$; while if $r_{MZ} = .8$ and $r_{DZ} = .2$, then $G = 1.20$ and $H = 0.75$. Similarly, when dealing with variances, the Holzinger H estimate may differ substantially from the conventional G estimate.

It was shown earlier that the concordance rate had to be expressed as a phenotypic correlation in liability between twins in making a genetic interpretation. Holzinger's index of heritability (H_C) is estimated directly from concordance rates,

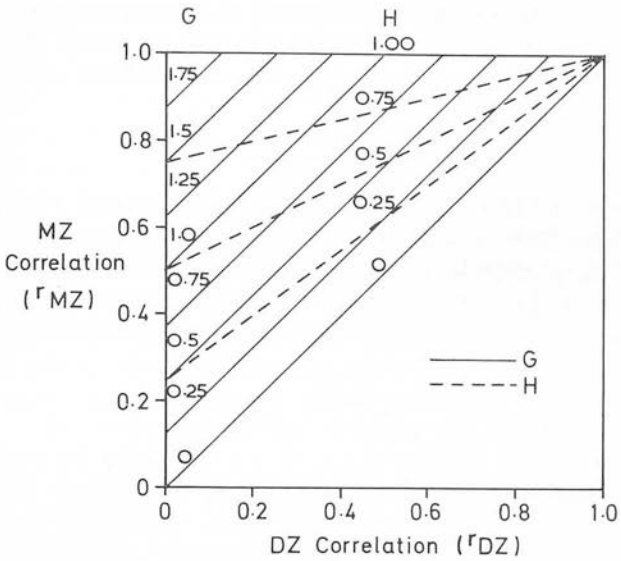

FIG. 2.—Estimates of the coefficient of genetic determination (G) and of Holzinger's index of heritability (H) from correlations in MZ and DZ twins. $G = 2(r_{MZ} - r_{DZ})$; $H = (r_{MZ} - r_{DZ}) / (1 - r_{DZ})$.

omits the above step, and leads to quite inappropriate results. This can be shown in figure 3 where the H_C estimate is usually much smaller than the G estimate. The values in figure 3 were calculated with $G = r_{MZ} = 2r_{DZ}$ from table 2. The graphs

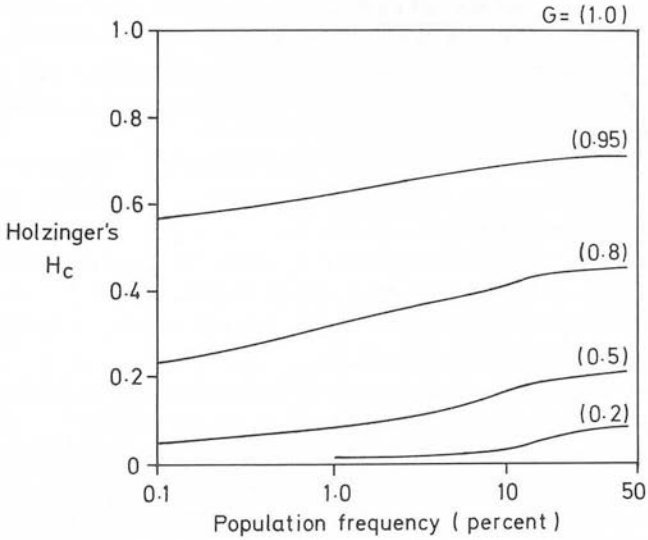

FIG. 3.—Values of Holzinger's H_C for various population frequencies (P) and coefficients of genetic determination (G), with $G = r_{MZ} = 2r_{DZ} = 2(r_{MZ} - r_{DZ})$.

show that the H_C index depends greatly on the population frequency and seriously underestimates the contribution of heredity in the expression of a trait. Other values of r_{MZ}, but with $G = 2(r_{MZ} - r_{DZ})$, were also used and similar results were obtained.

DISCUSSION

Interpretation of MZ concordance rates of less than unity has long perplexed human geneticists. Since, it is argued, MZ twins have the same genotype, a concordance rate of unity would be expected if the disease were entirely genetic. This is true for genetic markers but will not be the case if there is any variability in expression of the genotype, as in many traits and conditions, or if there are sporadic cases. Segregation analysis [15] of the twin pairs as families of size two is then the appropriate method of analysis estimating concurrently the penetrance, proportion of sporadic cases, level of ascertainment, and the segregation ratio.

In familial conditions with multifactorial inheritance, the concordance rate depends on the population frequency as well as on the correlation in liability between twins [7]. If the population frequency is low, the concordance rate in MZ twins will also be low even though there is a high correlation between the twins. Thus the apparent dilemma of low MZ concordance rates for rare ($<1\%$) and "common" (1%–5%) conditions which are thought to be largely genetic in origin can be readily explained.

Study of MZ and DZ twins provides a useful tool in assessing the role of heredity in the expression of human traits, but it is not surprising that the evidence from twins has not been as compelling as might be expected. Different authors collect their data in different ways, present their results in different forms, use different methods of analysis, and use different forms of genetic interpretation. Thus the results and their interpretations are usually not comparable in different studies, and often they are not meaningful in genetic terms. Moreover, only rarely are the sampling errors of the estimates computed, and so the degree of confidence to be put in any set of results is not known.

To remedy this situation, a standard form of analysis and reporting of twin studies is proposed based on the results developed in the previous sections. The suggested rules of procedure are:

1. Measure the population frequency (P) using the same criteria for diagnosis and ascertainment as for the individual twin probands.
2. Measure the *proband* concordance rate (P_R) in cotwins, counting pairs once for each member individually ascertained.
3. Measure the population frequency (P') appropriate for cotwins, using the same criteria for diagnosis and ascertainment as for the cotwins.
4. Estimate r_{MZ} and r_{DZ}, the correlations in liability for MZ and for DZ twins.
5. Estimate the standard errors of the correlations.
6. Derive the estimate of the coefficient of genetic determination (G) as $2(r_{MZ} - r_{DZ})$ with its standard error.

These rules present a minimal set of data and analysis for presentation of genetic

results in twins. Adjustment of the frequencies (P, P_R, and P') for incomplete ascertainment may also be required. The rationale and examples of the different steps are given in detail in the paper.

There are many other problems in research with twins which are not discussed here, such as zygosity diagnosis, analysis of like-sexed versus unlike-sexed twins, and assortative mating, and other problems which are common to all genetic analyses of familial data. Moreover, while concordance rates in twins can be very informative about the role of heredity in familial traits and conditions, they are unlikely ever to be critical in discriminating among different modes of inheritance. Even when data from twins are analyzed in combination with data from other kinds of relatives, discrimination will still be difficult [9, 16, 17].

SUMMARY

Proband concordance rates in twins provide estimates of correlation among twins in liability to a trait or condition. The correlations in turn can be interpreted genetically by the expression $2(r_{MZ} - r_{DZ})$ which eliminates nongenetic familial effects on twins and estimates the coefficient of genetic determination for the trait. The rates of diagnosis and of ascertainment of individuals and their cotwins must also be taken into account, along with other factors such as differences in frequency between sexes, variable age of onset, and variable expressivity or severity. A set of rules for the minimal set of data required and for a standard form of analysis is presented.

The genetic interpretation of other measures of concordance is difficult and their value is questionable. The indices of "heritability" proposed by Holzinger [14], widely used by human geneticists, are shown to be unsatisfactory and their use should be discontinued.

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A GENETIC REGISTER SYSTEM (*RAPID*)

BY

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A genetic register system (*RAPID*)

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Summary. Justification is given for establishing a genetic register system as a means of ascertaining and preventing genetic disease. Such a computerized register system, referred to by the acronym '*RAPID*' (*R*egister for *A*scertainment and *P*revention of *I*nherited *D*isease), has been established in Edinburgh.

The system involves ascertaining individuals in the population at risk of having a child with a serious genetic disorder through various record systems and statutory registers. Procedures for contacting and following up individuals found to be at risk are discussed.

Computer methods for the recording, storage, and retrieval of individual and family data are described.

Because of population mobility and the geographical dispersal of family members a Genetic Register System is more likely to be effective if organized on a national basis and the authors would therefore welcome the collaboration of other geneticists in this venture.

The effect of genetic counselling in reducing the proportion of cases of genetic disease in the population has been examined theoretically (eg, Smith, 1970; Motulsky, Fraser, and Felsenstein, 1971) and the results of such calculations have shown that unifactorial disorders offer the best scope in prevention. Genetic counselling would be expected to have much less effect in reducing the proportion of cases of multifactorial or chromosomal disorders because in general the number of individuals at high risk of having affected children in these families is small.

To gain some idea of the extent of the problem, families with *serious* genetic disorders referred to the Department of Human Genetics, Edinburgh, for counselling were studied. The results confirmed theoretical expectations that the main scope for preventing genetic disease lies with the simply inherited disorders (Emery and Smith, 1970). Secondly it was found that only a relatively small proportion (14%) of individuals at risk of having affected children (or carrier daughters in the case of X-linked disorders) in these families were referred specifically for genetic counselling (Emery, 1972). Many affected children were born to parents who, *a priori*, were at high risk of having affected children but had never been counselled and were therefore unaware of the risks. Others were referred for counselling only after the birth of an affected child which might otherwise have been prevented.

Thus it seemed to us that, on the basis of these findings, a greater proportion of cases of serious unifactorial disorders might be prevented if more individuals at risk in the population could be ascertained so that they might be given appropriate genetic advice. At present there is no defined procedure for tracing and following up such individuals, and it was decided that an answer to this problem might be found in the use of a genetic register system.

In recent years a number of investigators have argued the need for some form of genetic disease register (Miller, 1964; Newcombe, 1966; Renwick, 1968; McKusick, 1969; Wertelecki, Lawton and Gerald, 1969; Oliver, 1970; Welch, 1972). Most of these reports however, have been concerned with identifying affected individuals for welfare purposes or for research. Yet a more pressing problem is the need for a register system to help trace individuals at risk so that they can be counselled (Oliver, 1970;

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Welch, 1972). A recent report of a WHO Scientific Group (World Health Organization, 1972) has in fact recommended that medical genetics centres should set up registers of genetically determined disorders for this reason. Such a register was initiated in this Department in 1970, and is referred to by the acronym *RAPID*: *R*egister for the *A*scertainment and *P*revention of *I*nherited *D*isease. For ease of storage, updating, and retrieval of family data it has been necessary to computerize the register system.

Organization of a Genetic Register System

The first step in establishing the Genetic Register System was the *ascertainment* of individuals at high risk (greater than 1 in 10) of having a child with a serious genetic disorder where counselling would be appropriate. Ascertainment of such individuals depends primarily upon the detection of affected individuals within the population. This information may be obtained directly or indirectly. The more usual *direct* method of ascertainment may be through population screening programmes or as a result of routine diagnosis when a disorder is recognized to be genetic and the individual is then referred by the general practitioner or hospital consultant. With few exceptions (eg, phenylketonuria) population screening for unifactorial disorders is impractical because of their rarity. Individuals at risk can also be ascertained *indirectly* from data stored in other record systems and registers, such as hospital in-patient records, various public health records, and certain statutory registers (Fig. 1). The relative values of these various sources will be discussed later.

The second step in the genetic register system was the assessment of the risks of ascertained individuals having affected children. These risks are based upon genetic principles or empiric risks (Smith, Holloway, and Emery, 1971).

The third step was the development of procedures for contacting and following up individuals who were considered to be at high risk of having an affected child. This presents perhaps the most difficult problem. After careful consideration we have adopted the following procedures which we feel offer protection to the individual's right to privacy yet have proved practical in operation. In the case of families ascertained through individuals referred directly to the genetic clinic, other family members deemed to be at risk are contacted only with the express permission of the individual seen in

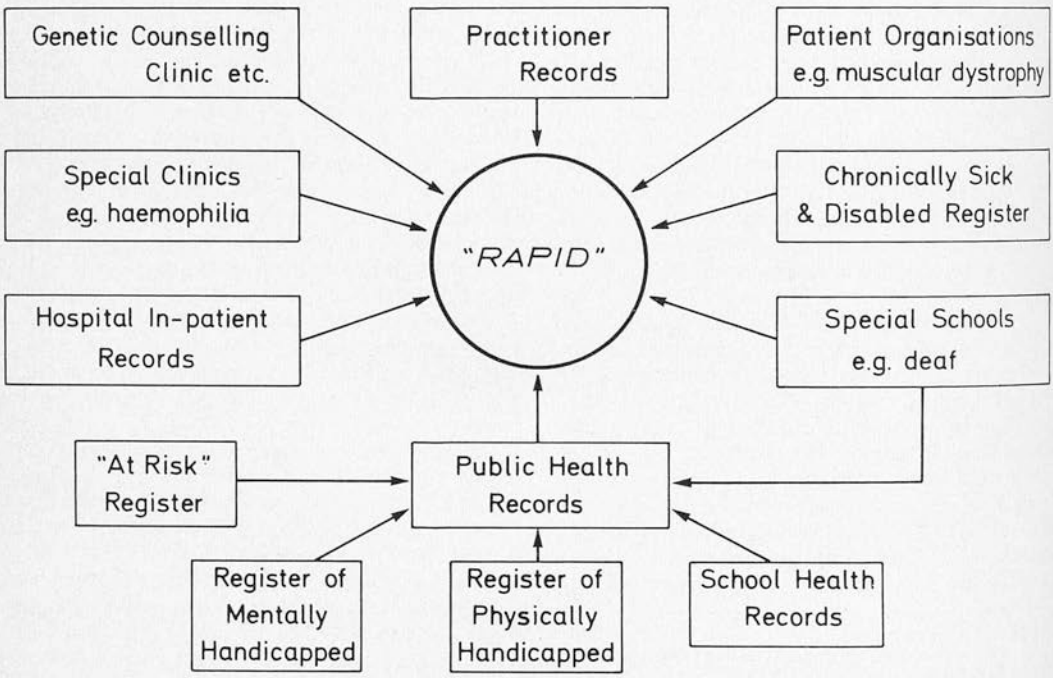

FIG. 1. Methods of ascertaining individuals and their families with serious genetic disorders.

the clinic. When this permission is given then relatives at risk are contacted, not directly, but through their general practitioner. This is considered important as there may be factors unknown to the geneticist or individual seen in the clinic which might make it unnecessary or even imprudent to contact certain family members. The relative's general practitioner can be identified provided the name and address of the relative is known because each local Executive Council (National Health Service) holds a list of patients in any particular area along with the practitioners with whom they are registered.

In the case of individuals ascertained in other ways, they are not approached without first obtaining the permission of their practitioner and often the consultant as well.

The problem whether individuals should be told they are at risk of having an affected child when this information has not been requested has recently been considered at length both from the ethical (Lappé, Gustafson, and Roblin, 1972) and scientific (Littlefield, 1972) points of view. We feel that parents have a right to know these risks. However, we also believe that the general practitioner is usually a good guardian of the individuals' interests in this regard. A discussion of the genetic risks and their implications first between the geneticist and the practitioner is therefore, in our opinion, the best approach to the problem. In the case of individuals ascertained indirectly through other registers and record systems it also allows the geneticist to determine how precisely a particular diagnosis has been established.

Recording, Storage, and Retrieval of Family Data

Data on all ascertained individuals and their relatives deemed to be at risk are recorded on specially designed cards. For each individual there are four cards (see Appendix): the first deals with personal details, the second with disease details, the third with medical (general practitioner, consultant, and hospital) details, and the fourth with genetic details. The information is vetted, encoded, and then stored in the computer file. A pedigree is taken at interview but this is not stored in the computer

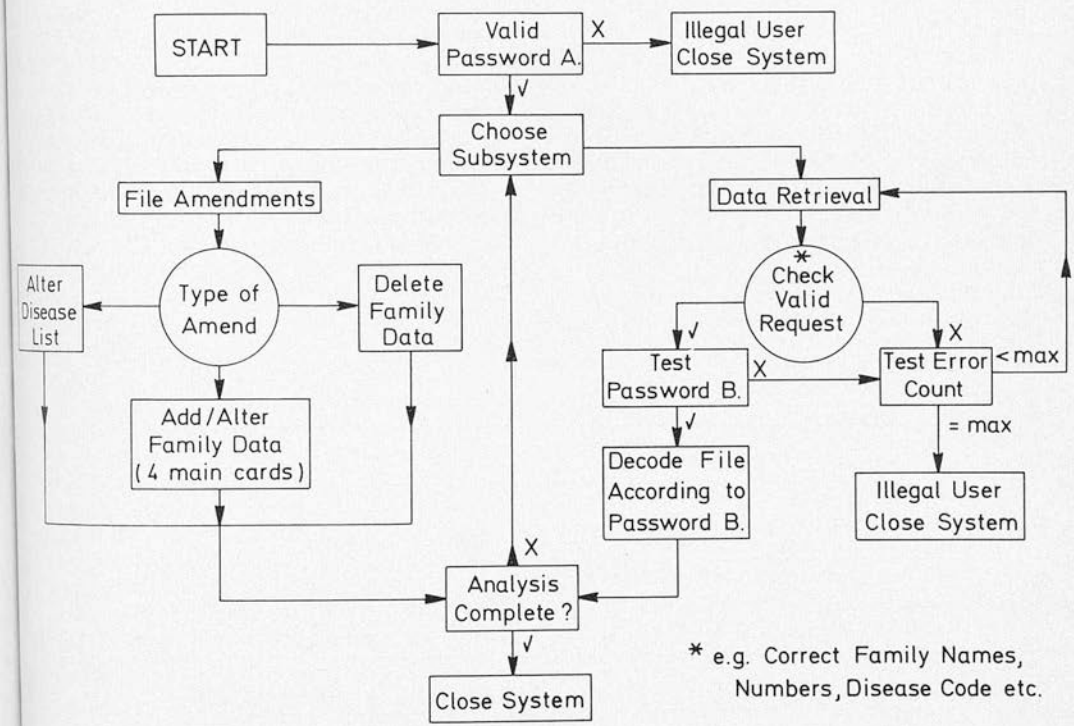

FIG. 2. Simplified outline of the *RAPID* system.

since it is not essential to the system, though this information can be computerized if necessary (Krush *et al*, 1970).

Each family is allotted a code number (eg, 247/–) and each individual at risk in the family is then numbered accordingly starting with the first individual contacted (eg, 247/1). Specific disorders are coded by adding a fifth digit to the code given in the International Classification of Diseases (ICD). This may prove somewhat restrictive in the future as the number of recognized genetic disorders increases but it has proved simple and convenient in use over the last 3 years. A coding based on the ICD has the advantage that it includes both multifactorial as well as unifactorial disorders. An example of the extended ICD coding is illustrated in the case of the spinal muscular atrophies (330·1):

Infantile type	330·11
Intermediate type	330·12
Juvenile type	330·13
Adult type	330·14
Distal type	330·15, etc.

The code numbers for families, individuals in the families, and diseases are used in all subsequent manipulations of the data. A computer program for recording and retrieving individual and family data has been produced, details of which are available (Moores, 1972). The file system is at present capable of storing data on between 25 and 30 thousand individuals. Access to the data is through a teletype terminal using the Edinburgh Multi-Access System (EMAS) on an ICL 4–75 computer.

Because of the need to maintain strict confidentiality of the information in the register a number of security checks have been incorporated into the system. Access to the system by anyone working with the register is only possible when a valid password A has been used (Fig. 2). One may then directly choose to amend the file data. Since this does not involve data retrieval, no further checks of this subsystem are necessary. If, however, the operator wishes to retrieve data the request must first be checked for its validity, ie, correct family names, numbers, and disease code, etc. A legitimate user may on occasion make an error, and for this reason an error count is introduced into the system. Finally, a second password B is needed. This allows data to be retrieved at different levels depending on the particular operator's password. For example the clinician dealing with a family has access to all the genetic and medical information on the individuals in the family. On the other hand a genetic field worker who is concerned with tracing relatives may only retrieve pedigree data.

It might be considered that such a system of checks is excessive. We feel it is necessary in view of the present justified concern over patient confidentiality, and particularly since information about inherited disease could be subject to possible misuse more than purely clinical information would be. For example, within the register there is information on individuals who, though perfectly healthy at present, may be at risk of developing a genetic disorder in the future (eg, myotonic dystrophy or Huntington's chorea). If this liability were known, perhaps to a prospective employer, this might be to the individual's disadvantage. Information about any individual in the register is only released to physicians and medical geneticists who are directly involved in the management of the patient and his family.

TABLE I

SOURCES OF RECORDS SURVEYED FOR SERIOUS GENETIC DISORDERS AND NUMBERS OF INDIVIDUALS SELECTED FOR CONTACT THROUGH THE REGISTER SYSTEM

(Psychiatric disorders excluded)

Source	Period Covered	No. of Records Surveyed	No. Selected
*Hospital Admissions**	1970–71		
Adult		17,628	117 (0·7%)
Children		4325	67 (1·5%)
Total		21,953	184 (0·8%)
Public Health Registers (City of Edinburgh)			
'At risk'	1964, 1969–70	4837	68 (1·4%)
Mentally handicapped	1964, 1967–72	285	33 (11·6%)
Physically handicapped	1964, 1967–72	180	53 (29·4%)
Chronically sick and disabled	1972–73	4868	161 (3·3%)
Special Schools			
Donaldson's School for the Deaf, Edinburgh	1960–67	150	26 (17·3%)

* Western General Hospital, Edinburgh.

Feasibility of a Genetic Register System

The feasibility of various aspects of the *RAPID* system is currently under investigation, but limited so far to individuals and their families residing in this region.

An attempt has been made to assess which sources of patient data are likely to yield the greatest number of individuals at risk of having affected children. Obviously special clinics for particular genetic disorders (eg, haemophilia) and referrals to the genetic clinic yield a large number of families in which there are individuals at risk (Emery and Smith, 1970). Screening of other registers and record systems, by ICD coding and diagnostic classification of diseases likely to include genetic disorders (Table I), indicates that some sources (eg, registers for the mentally and physically handicapped) may be potentially more fruitful than others (eg, 'at risk' registers). School health records have been found to be a relatively poor source of material because of the comparative lack of information on which to delineate genetic disorders.

It is to be expected that the comparative proportions of ascertained individuals with serious genetic disorders will vary with the designation and catchment area of a particular hospital and will probably be greatest in the case of children's hospitals. However, within this region our experience indicates that general hospitals can be usefully surveyed when statistics are computerized and facilities exist to examine relevant case records.

The ascertainment, tracing, and contacting of individuals who had been previously seen in the genetic department has been comparatively easy because, detailed information was already known about them. We have so far been able to trace over 80% of those individuals who we have wished to contact. Of these almost all have been co-operative and where relevant (ie, with a relative at high risk residing in this region) have given permission for their relatives to be approached.

With regard to individuals ascertained from sources other than the genetic department, as would be expected many were unaware of the full implications of the heritable nature of their disorder. Nevertheless after discussion permission to approach relatives has so far been obtained in over three quarters of these cases.

These are preliminary findings and it is appreciated that much more information will be needed to determine fully the feasibility of the register system.

Further Uses of a Genetic Register System

Apart from the prevention of genetic disease, a genetic register system could be valuable in a number of other ways which have been enumerated by McKusick (1969). By ascertaining individuals at risk of developing a serious genetic disorder, or at risk of having affected children, this could lead to early and correct diagnosis and even the institution of proper treatment in rare genetic disorders. It could also be of value in alerting individuals with inherited susceptibilities to drugs and for detecting and eradicating life-threatening complications of genetic disease, such as intestinal malignancy in polyposis coli. Many of these functions, however, might only be realized if a genetic register system were linked to other health records.

A linked system of health records has been advocated for many purposes (Acheson, 1967) including the prevention of genetic disease (Welch, 1972). Linkage of various hospital and public health records with a genetic register system could be valuable in a number of ways. For example, through linkage with hospital in-patient records, information on an individual known to be at risk of developing a serious genetic disorder could be made available to the hospital consultant which might be helpful in diagnosis and management of the patient. However, though linkage with other health records could be valuable, many of the functions of a genetic register system in disease prevention are not dependent on such linkage.

Finally, because of population mobility and the geographical dispersal of family members, a genetic register system is more likely to be effective if organized on a national basis. Collaboration between genetic centres in different parts of the country would therefore be important.

It is a great pleasure to acknowledge all those who, at one time or another, have played a part in developing this system particularly Miss Susan Holloway, BSc, and Miss Moira Young, SRN. We are also grateful for the invaluable help of Dr J. L. Gilloran, Dr M. A. Heasman, Dr H. E. Seiler and their respective staffs, and Mr W. Jeffrey, Principal of Donaldson's School, Edinburgh.

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APPENDIX

'*RAPID*' CLINICAL RECORD CARDS

Card 1—Personal Details

Field Content		Cols	Coding
Card number		1	1
Family number		2–6	
Individual number		7–8	
Old/new record		9	O—Old, N—New
Title		10–13	Miss, Mrs, Mr
First name		14–21	
Second initial		22	
Surname		23–33	
Sex		34	M—Male, F—Female
Marital status		35	S—Single, M—Married, W—Widowed, D—Divorced, Z—Not known
Birth	Day	36–37	
	Month	38–39	
	Year	40–41	
Father's initials (if a child)		42–43	
Address (+ postal code)		44–72	

Card 2—Disease Details

Field Content	Cols	Coding
Card number	1	2
Family/Individual number	2–9	As for card 1
Disorder	10–28	
Code number	29–33	
Mode of inheritance	34–35	AD—Autosomal dominant AR—Autosomal recessive XR—X-linked CH—Chromosomal CX—Complex, multifactorial NR—Not resolved NI—Not inherited ZZ—Not known
Code number for any other disorder	36–40	

Field Content		Cols	Coding
Mode of inheritance		41–42	
Data ascertained	Month	43–44	
	Year	45–46	
How ascertained		47–48	GP—Practitioner CO—Consultant GR—Genetic register, etc SE—Self
Number of affected relatives			
Parents		49	
Sibs		50	
Uncles, aunts		51	
Nephews, nieces		52	
Grandparents		53	
Grandchildren		54	
Cousins		55	

Card 2—Disease Details—*continued*

Field Content		Cols	Coding
Self		56	A—Affected H—High risk of being affected L—Low risk of being affected N—Not at risk
Number of living children:	Affected	57	
	At risk	58	
	Normal	59	
Number of dead children:	Affected	60	
	Normal	61	
Adopted children		62	
Information up-to-date		63	N—No D—Dead
Future children:	Risk	64	H—High M—Medium L—Low N—Not at risk
	%	65–66	
Follow-up	By	67	G—GP C—Consultant F—Family
	Reason	68	D—Diagnosis C—Counselling V—Review
Date of follow up	Month	69–70	
	Year	71–72	

Card 3—Medical Details

Field Content		Cols	Coding
Card number		1	3
Family/individual number		2–9	As for card 1
General practitioner			
Initials		10–11	
Surname		12–22	
Address		23–45	
Contacted		46	Y, N
Attitude		47	U—Uncooperative I—Indifferent C—Cooperative
Hospital code		48–49	
Patient Hospital number		50–55	
Consultant			
	Title	56–57	
	Initials	58–59	
	Surname	60–70	
Contacted		71	Y, N
Attitude		72	As for col. 47

Card 4—Genetic Details

Field Content		Cols	Coding
Card number		1	4
Family/individual number		2–9	As for card 1
Employment		10–21	
Social class		22	
Father's birth year		23–24	
Mother's birth year		25–26	
Maiden name		27–34	
Own or mother's maiden name		35	
Visit details			
Visit	Number	36	
Date	Day	37–38	
	Month	39–40	
	Year	41–42	
Seen	By	43–44	Clinicians initials
	For	45–46	DI—Diagnosis CO—Counselling FO—Follow-up OT—Other
	At	47–48	As for card 3 (cols. 48–49)
Counselling	Advice (1)	49–50	RE—Reassurance SA—Selective abortion AI—Artificial insemination, etc
	Advice (2)	51–52	
	Method	53–54	FL—Family limitation ST—Sterilization AB—Abortion SA—Selective abortion, etc
	Attitude	55	As for card 3 (col. 47)
Children wanted		56	Y, N
Comments		57–70	
Race		71	C—Caucasian N—Negro M—Mongolian, etc
Religion		72	P—Protestant C—Catholic J—Jewish, etc

Letters to the Editor

SOME IMPLICATIONS OF HL-A AND DISEASE ASSOCIATIONS

SIR,—The numerous reports of associations between the histocompatibility loci (HL-A) and various familial diseases have important implications in medical genetics. Some of the confirmed associations [1,2] are summarised in the accompanying table, but at least another 10 conditions

SUMMARY OF CONFIRMED ASSOCIATIONS OF HL-A TYPE WITH SEVERAL FAMILIAL DISEASES

Disease	HL-A type	No. of reports	No. of cases	Percentage with HL-A type	
				Cases	Controls
Ankylosing spondylitis[1] ..	27	2	115	93	5
Acute anterior uveitis	27	2	61	59	5
Reiter's disease ..	27	1	33	76	9
Coeliac disease[1] ..	8	8	525	79	27
Dermatitis herpetiformis ..	8	2	63	63	29
Myasthenia gravis..	8	2	63	57	21
	1	2	63	56	25
Psoriasis	13	2	200	18	5
	W17	2	200	25	6
Multiple sclerosis* ..	3	1	107	37	25
	7	1	107	40	26
	LD-7a†	1	28	70	16

[1] Not confirmed. † Lymphocyte-defined determinant.

have also been associated with HL-A loci. Some implications are:

1. *Strength of association.*—These HL-A associations are much stronger than any found previously with other genetic markers, such as the blood-groups (see table).

2. *Genetic disease.*—The HL-A associations show that these familial diseases have an important and identifiable genetic component. This widens the definition of genetic disease from that due to rare abnormal genes to that due (at least partly) to common genes at intermediate frequencies. These represent a class of genes which was not previously regarded as important in medical genetics.

3. *Homozygotes.*—Individuals affected by the diseases studied seem to be predominantly heterozygotes for the HL-A type involved, rather than homozygotes. Are homozygotes not at greater risk? Or do they manifest another more severe form of disease?

4. *Penetrance.*—Only a small proportion of individuals with the HL-A type involved seem to manifest the condition. Thus penetrance is usually low—e.g., 8% in males and 1% in females in ankylosing spondylitis.[1] Such low penetrance-rates for a single locus have not been previously reported in man.

5. *Resolution of heterogeneity.*—Using the HL-A type as a genetic marker it may be possible to split up a disease into different genetic (and non-genetic) groups, so resolving any heterogeneity.[3]

6. *Association of different disorders.*—The same HL-A type may be involved in a group of associated disorders (see table). The pattern of familial associations, risks, and causes for the different conditions may then be understood and exploited.

7. *Groups at risk.*—Identifying groups at risk through their HL-A type may be useful in the following ways: in initial screening for individuals with preclinical symptoms; in epidemiological research; and in genetic counselling.

8. *Genetic models.*—Demonstration of a locus with a major effect on several disorders but with low penetrance will influence the choice of models in genetic analysis. It has proved difficult to discriminate between multifactorial and unifactorial models when low penetrance.[4] More powerful statistical methods are being developed.[5,6] A crucial test of their utility will be whether they can demonstrate unequivocally a major locus effect for diseases with a known HL-A association.

Other aspects involve the nature and cause of these associations, their selective effects, and the origins and maintenance of the HL-A polymorphisms. Clearly the HL-A associations promise many applications in medical genetics.

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RISK TABLES FOR GENETIC COUNSELLING IN SOME COMMON CONGENITAL MALFORMATIONS

BY

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Risk tables for genetic counselling in some common congenital malformations

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Summary. Tables of estimated recurrence risks for some 180 specific family histories are presented for three common congenital malformations. It is hoped that the tables will provide standards and be useful in genetic counselling.

In genetic counselling, estimation of recurrence risks for the common congenital malformations depends on the empiric risks since the mode of inheritance is usually not known. However, the recurrence risk in any particular family depends on the family history, the sex of affected individuals, on the severity of the disease in the family, and on several other factors. The object of this paper is to describe the derivation of a set of tables of recurrence risks estimated from a multifactorial model of liability to the malformation (Falconer, 1965/1966). It is hoped that these tables will be useful to clinicians and provide standards for genetic counselling in these disorders.

Material

To estimate recurrence risks with the multifactorial model two statistics are required, namely the frequency of the condition in the population and the frequency in first-degree relatives of affected individuals. Data on these for three common congenital malformations in England are given in Table I. Estimates of the correlation in liability between first-degree relatives can be read from Fig. 1 in Smith (1970/1971) or derived from formula (3) in Reich, James, and Morris (1972/1973).

A method to derive the recurrence risks with the multifactorial model has been given by Smith (1971a). Information about affected first-, second-, and third-degree relatives and about unaffected relatives can be included. The method can handle differences in frequency between sexes and take account of different severity-age classes. The computer program RISKMF (Smith, 1972) is used to derive the risk estimates. Details of family history are given, listing for each person the sex, disease status, and relationship to the person at risk.

The number of possible family histories that could be considered had to be limited. Preliminary trials showed that inclusion of unaffected second- and third-degree relatives was not important in affecting the recurrence risks. Moreover, for first-degree relatives, the change in recurrence risk with n normal relatives was approximately n times the change for one normal relative. Thus a wide variety of families with n normal relatives could be covered by extrapolation. Similarly, the sex of affected second and third degree relatives did not affect the risks very much, so could be ignored. By contrast, the risks were influenced to a much greater extent by whether affected individuals were on one or on both sides of the pedigree, so this was taken into account.

Results

The estimated recurrence risks for the three congenital malformations in Table I are given in Tables II, III, and IV; these tables are in the form of output by the computer. Each table lists the malformation studied, the author, country and date of the report, the frequency for each sex and for sexes combined, and the estimated correlation in liability between first-degree relatives. There are four main columns, for the four possible parental types, and 27 rows for the various family histories within parental type. Each main column is separated into two secondary columns giving the risks with a paternal or with a maternal relative affected.

As an example of extrapolation to other families consider a family with cleft lip $\pm$ cleft palate (Fig. 1). The nearest situation is line 11, Table II, with a risk of 21·6% (ignoring the paternal affected relative). The existence of two unaffected sibs lowers the risk by $2 \times 2{\cdot}2\%$ (line 12–line 13), while the existence of the affected paternal relative increases

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TABLE I

FREQUENCIES OF THREE COMMON MALFORMATIONS IN ENGLAND, AND ESTIMATES OF THE CORRELATION IN LIABILITY AMONG FIRST-DEGREE RELATIVES

Malformation	Author	Population Frequency (%)			Frequency in First-degree Relatives (%)	Correlation in Liability
		All	Males	Females		
Cleft lip ± cleft palate	Carter (1965; 1969)	0·10	0·13	0·07	3·1 (S, O)	0·42 ± 0·020
Pyloric stenosis	Carter and Evans (1969)	0·30	0·50	0·10	4·0 (S, O, P)	0·37 ± 0·013
Anencephaly and spina bifida	Carter and Evans (1973)	0·29	0·21	0·38	4·4 (S)	0·39 ± 0·019

S = sibs; O = offspring; P = parents.

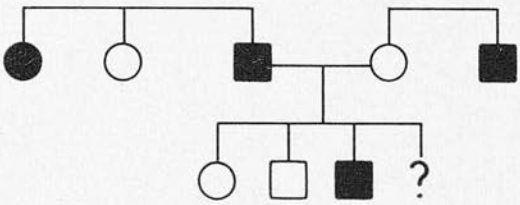

FIG. 1.

TABLE II

RECURRENCE RISKS (%) FOR MULTIFACTORIAL INHERITANCE
Cleft lip (+ or −) cleft palate in England (Carter, 1965; 1969)

	Parents							
	Neither Affected		Father Affected		Mother Affected		Both Affected	
	Pat	Mat	Pat	Mat	Pat	Mat	Pat	Mat
No sibs	0·1		3·0		3·5		35·4	
1 sib U	0·1		2·8		3·2		32·3	
1 M sib A	2·6		10·0		10·8		40·8	
1 F sib A	3·1		10·9		11·8		41·6	
1 F sib A + 1 sib U	2·9		9·8		10·6		38·9	
2 M sibs A	8·1		18·1		18·9		44·4	
1 M + 1 F sibs A	8·8		19·1		19·9		45·1	
2 F sibs A	9·5		20·1		20·9		45·7	
2 F sibs A + 1 sib U	8·8		18·2		18·9		43·1	
1 2nd-degree relative A	0·6	0·7	3·8	12·4	13·6	4·4	40·0	40·0
1 M sib + 1 2nd A	5·2	5·3	11·4	21·6	22·8	12·1	44·7	44·2
1 F sib + 1 2nd A	5·9	6·1	12·4	22·7	23·9	13·1	45·4	44·9
1 F sib + 1 2nd A + 1 sib U	5·4	5·6	11·1	20·5	21·6	11·8	42·6	42·1
2 sibs + 1 2nd A	13·1	13·3	21·0	29·6	30·3	21·5	48·6	48·0
2 sibs + 1 2nd A + 1 sib U	11·9	12·2	19·1	27·3	28·1	19·6	45·6	45·1
1 3rd-degree relative A	0·3	0·3	3·6	6·4	7·3	4·1	38·7	38·8
1 M sib + 1 3rd A	3·8	3·9	11·0	15·0	16·0	11·7	43·5	43·2
1 F sib + 1 3rd A	4·4	4·5	11·9	16·0	17·1	12·7	44·3	43·9
1 M sib + 1 pat 2nd + 1 3rd A	6·3	7·8	12·3	17·0	27·5	24·4	47·2	47·2
1 M sib + 1 mat 2nd + 1 3rd A	7·9	6·6	23·4	26·4	17·8	12·9	47·0	46·3
1 F sib + 1 pat 2nd + 1 3rd A	7·1	8·6	13·3	18·1	28·6	25·6	47·9	47·9
1 F sib + 1 mat 2nd + 1 3rd A	8·7	7·4	24·6	27·6	18·9	13·9	47·7	47·0
1 F sib + 1 3rd A + 1 sib U	4·1	4·2	10·7	14·3	15·3	11·4	41·4	41·2
2 sibs + 1 3rd A	11·2	11·4	20·5	24·4	25·0	21·1	47·5	47·1
2 sibs + 1 3rd A + 1 sib U	10·3	10·4	18·6	22·2	22·9	19·2	44·6	44·3
2 sibs + 1 pat 2nd + 1 3rd A + 1 sib U	13·4	15·1	19·9	24·0	31·8	29·5	47·8	47·8
2 sibs + 1 mat 2nd + 1 3rd A + 1 sib U	15·2	13·8	28·9	31·0	24·5	20·3	47·6	47·0

	Both Sexes	*Males*	*Females*
Frequency (%)	0·10	0·13	0·07
Correlation between first-degree relatives (%)	42·0	42·0	42·0

M = male; F = female; A = affected; U = unaffected; pat = paternal; mat = maternal.

TABLE III

RECURRENCE RISKS (%) FOR MULTIFACTORIAL INHERITANCE
Congenital pyloric stenosis in England (Carter and Evans, 1969)

	Parents							
	Neither Affected		Father Affected		Mother Affected		Both Affected	
	Pat	Mat	Pat	Mat	Pat	Mat	Pat	Mat
No sibs	0·3		3·7		5·1		29·8	
1 sib U	0·3		3·4		4·7		27·1	
1 M sib A	3·2		10·2		12·1		35·3	
1 F sib A	4·6		12·8		14·8		37·8	
1 F sib A+1 sib U	4·3		11·6		13·5		34·9	
2 M sibs A	8·6		17·3		19·0		39·6	
1 M+1 F sibs A	10·7		20·2		21·7		42·0	
2 F sibs A	13·0		23·1		24·5		44·2	
2 F sibs A+1 sib U	11·9		21·0		22·5		41·2	
1 2nd-degree relative A	1·1	1·2	5·1	11·0	13·6	6·7	35·4	44·9
1 M sib+1 2nd A	5·7	6·1	12·4	18·8	21·2	14·1	40·5	39·6
1 F sib+1 2nd A	7·6	8·1	15·3	21·9	24·1	16·9	43·0	42·0
1 F sib+1 2nd A+1 sib U	7·0	7·5	13·7	19·8	22·0	15·3	39·8	39·0
2 sibs+1 2nd A	13·5	14·1	21·7	27·6	29·1	22·9	45·9	44·8
2 sibs+1 2nd A+1 sib U	12·4	13·0	19·7	25·1	26·8	20·9	42·6	41·7
1 3rd-degree relative A	0·6	0·6	4·5	6·8	8·8	6·1	33·1	33·0
1 M sib+1 3rd A	4·5	4·7	11·5	14·4	16·6	13·4	38·4	38·0
1 F sib+1 3rd A	6·2	6·4	14·3	17·4	19·5	16·2	41·0	40·5
1 M sib+1 pat 2nd+1 3rd A	7·0	8·2	13·7	17·2	25·4	23·1	43·6	43·4
1 M sib+1 mat 2nd+1 3rd A	8·4	7·8	20·9	23·3	19·1	15·2	42·9	42·0
1 F sib+1 pat 2nd+1 3rd A	9·2	10·6	16·7	20·5	28·4	26·1	46·0	45·8
1 F sib+1 mat 2nd+1 3rd A	10·8	10·1	24·2	26·5	22·2	18·1	45·3	44·3
1 F sib+1 3rd A+1 sib U	5·7	5·9	12·9	15·7	17·7	14·7	37·8	37·5
2 sibs+1 3rd A	11·9	12·3	20·8	23·7	25·2	22·1	44·0	43·4
2 sibs+1 3rd A+1 sib U	11·0	11·3	18·8	21·5	23·1	20·3	40·8	40·4
2 sibs+1 pat 2nd+1 3rd A+1 sib U	14·0	15·4	21·0	24·2	30·3	28·5	45·2	45·0
2 sibs+1 mat 2nd+1 3rd A+1 sib U	15·6	15·0	27·1	29·0	25·4	21·9	44·6	43·7

	Both Sexes	*Males*	*Females*
Frequency (%)	0·30	0·50	0·10
Correlation between first-degree relatives (%)	37·0	37·0	37·0

the risk by 1·4% (line 11–line 3). Putting these together gives an approximate risk of 18·6%.

Discussion

The basic assumption underlying these risk estimates is that there is underlying continuous liability to the malformations. The derivation of the recurrence risks then depends on the estimated *phenotypic* correlation in liability among first-degree relatives. A genetic interpretation is not necessary (though the correlations among different relatives are assumed to be proportional to their degree of genetic relationship) so the methods apply to any familial disease with an underlying liability.

Other methods of estimating recurrence risks have been proposed. Morton (1969) suggested that where risks were variable between sibships, the distribution of risks may be represented by a beta distribution. Smith (1971a) compared risks estimated from the beta distribution and from the multifactorial model and found good agreement for the two models. Similarly, it is difficult in practice to discriminate between a multifactorial model and a unifactorial model with incomplete penetrance since the different modes of inheritance lead to similar frequencies in relatives (Smith, 1971b). Thus the choice of the correct model in estimating recurrence risks may not be critical, because different models lead to substantially the same risk estimates. The merits of the risk tables presented here may be that the risks are derived in a clearly defined manner and so may provide useful standards for genetic counselling. Eventually when sufficient data has accumulated on families with these congenital abnormalities, the reliability of the estimated risks can be assessed, and their accuracy further improved.

Tables have also been derived for a further eight congenital abnormalities (cleft palate, club-foot, dislocation of the hip, Hirschsprung's disease, coeliac disease, aortic stenosis, atrial septal defect, and ventricular septal defect) and are available on request. However, there is considerable variation in the frequency of all these congenital abnormalities among regions, countries, and races. Tables of risks appropriate to a particular genetic counselling

TABLE IV

RECURRENCE RISKS (%) FOR MULTIFACTORIAL INHERITANCE
Spina bifida + anencephaly in England (Carter and Evans, 1973)

	Parents							
	Neither Affected		Father Affected		Mother Affected		Both Affected	
	Pat	Mat	Pat	Mat	Pat	Mat	Pat	Mat
No sibs	0·3		4·9		4·3		32·7	
1 sib U	0·3		4·5		4·0		29·8	
1 M sib A	4·2		13·9		13·0		39·3	
1 F sib A	3·6		12·8		11·9		38·4	
1 F sib A + 1 sib U	3·4		11·6		10·8		35·4	
2 M sibs A	11·5		23·0		22·4		44·5	
1 M + 1 F sibs A	10·6		21·8		21·1		43·7	
2 F sibs A	9·8		20·6		19·9		43·0	
2 F sibs A + 1 sib U	9·0		18·8		18·1		39·9	
1 2nd-degree relative A	1·2	1·2	6·3	14·0	12·9	5·6	37·5	37·8
1 M sib + 1 2nd A	7·4	7·2	15·9	23·7	22·7	15·2	43·4	43·8
1 F sib + 1 2nd A	6·6	6·5	14·7	22·5	21·4	14·0	42·5	42·9
1 F sib + 1 2nd A + 1 sib U	6·1	5·9	13·2	20·4	19·4	12·5	39·3	39·6
2 sibs + 1 2nd A	14·4	14·2	23·5	30·1	29·4	23·1	47·1	47·6
2 sibs + 1 2nd A + 1 sib U	13·2	13·0	21·4	27·6	26·9	20·9	43·8	44·2
1 3rd-degree relative A	0·6	0·6	5·8	8·7	7·8	5·1	35·8	35·9
1 M sib + 1 3rd A	5·9	5·8	15·2	18·8	17·9	14·4	42·0	42·2
1 F sib + 1 3rd A	5·2	5·1	14·1	17·5	16·6	13·3	41·1	41·3
1 M sib + 1 pat 2nd + 1 3rd A	9·1	10·2	17·2	21·3	27·2	24·9	45·9	46·3
1 M sib + 1 mat 2nd + 1 3rd A	10·1	8·7	25·8	28·2	20·6	16·5	46·6	46·6
1 F sib + 1 pat 2nd + 1 3rd A	8·2	9·2	15·9	20·0	26·0	23·5	45·1	45·5
1 F sib + 1 mat 2nd + 1 3rd A	9·1	7·9	24·5	26·9	19·2	15·3	45·8	45·8
1 F sib + 1 3rd A + 1 sib U	4·8	4·7	12·7	15·8	14·9	11·9	37·9	38·1
2 sibs + 1 3rd A	12·8	12·6	22·9	26·1	25·5	22·3	45·9	46·2
2 sibs + 1 3rd A + 1 sib U	11·7	11·6	20·8	23·8	23·1	20·2	42·7	42·8
2 sibs + 1 pat 2nd + 1 3rd A + 1 sib U	15·0	16·0	22·5	26·0	30·6	28·8	46·0	46·4
2 sibs + 1 mat 2nd + 1 3rd A + 1 sib U	16·0	14·6	29·4	31·3	25·6	22·1	46·6	46·7

	Both Sexes	*Males*	*Females*
Frequency (%)	0·29	0·21	0·38
Correlation between first-degree relatives (%)	39·0	39·0	39·0

area can be produced on request (cost about £10) by providing us with the population frequency (two sexes) and the frequency in first degree relatives for the area concerned. For more exact risks, to include information on severity of cases or for still more complex families the program RISKMF can be used directly.

The idea of producing a set of risk tables came from Dr A. Czeizel, Hungary, who derived a set of tables of risks for sibships with congenital abnormalities from Hungarian data. We would like to thank Professor A. E. H. Emery for encouraging us to produce the Tables in the form presented here.

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LINKAGE BETWEEN THE LOCI FOR BENIGN (BECKER-TYPE) X-BORNE MUSCULAR DYSTROPHY AND DEUTAN COLOUR BLINDNESS

BY

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Linkage between the loci for benign (Becker-type) X-borne muscular dystrophy and deutan colour blindness

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Summary. A family is described in which benign Becker type X-linked muscular dystrophy and deutan colour blindness are segregating. The lod scores from this family have been added to those obtained in a family previously reported (Emery *et al*, 1968/1969) and give an estimate of 0·23 for the recombination fraction with 95% confidence limits of 0·13 to 0·43. These results confirm the linkage relationships between deutan colour blindness and Becker muscular dystrophy but since the loci for Duchenne muscular dystrophy and colour blindness are not within measurable distance of each other these results indicate that the Becker and Duchenne types of X-linked muscular dystrophy are not allelic.

Besides the severe Duchenne type of muscular dystrophy, there is a more benign form of X-linked muscular dystrophy first described by Becker (Becker and Kiener, 1955; Becker, 1957, 1962). In this latter disorder proximal muscle wasting and weakness first becomes evident in late childhood, the teens or early adult life and affected individuals usually survive at least into middle age.

Previous studies have shown that the loci for Duchenne muscular dystrophy and the Xg blood groups (Clark *et al*, 1963; Blyth *et al*, 1965; Filippi and Macciotta, 1967) and colour blindness (Emery, 1966) are not within measurable distance of each other. Further, the loci for Becker muscular dystrophy and the Xg blood groups are not closely linked (Emery, Smith, and Sanger, 1968/1969). However studies of one large family with this disorder in which deutan colour blindness was segregating, showed that the maximum likelihood estimate of the recombination fraction for these two loci was 0·28 (Emery *et al*, 1968/1969). These results suggest that the loci for the Becker and Duchenne types of muscular dystrophy may not be allelic. However the confidence limits for the recombination fraction were wide (0·15 to 0·50). There was therefore a need to study further families with Becker muscular dystrophy for possible linkage with colour blindness.

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In a survey of patients with Becker muscular dystrophy another family in which deutan colour blindness was segregating has been discovered, and the original family has been extended. The results of linkage studies in these two families are reported in the present communication.

Subjects

Details of the first family in which deutan colour blindness was segregating have been reported previously (Emery *et al*, 1968/1969). The diagnosis of muscular dystrophy in the second family was confirmed by a muscle biopsy on the proband, the histology of which was consistent with the diagnosis of muscular dystrophy. Serum levels of creatine kinase were determined on all apparently unaffected males in this family since it is known that preclinical cases of Becker type muscular dystrophy can be detected in this way (Rotthauwe and Kowalewski, 1966; Emery, 1968). In none of the families studied were early contractures a prominent feature of the disease unlike the family described by Thomas, Calne, and Elliott (1972) in which deutan colour blindness was also segregating.

Methods

Serum levels of creatine kinase were determined on fresh specimens of blood by the method described by Rosalki (1967).

Colour vision was tested using the Ishihara plates and the AO-HRR (American Optical Hardy-Rand-Rittler) pseudoisochromatic plates.

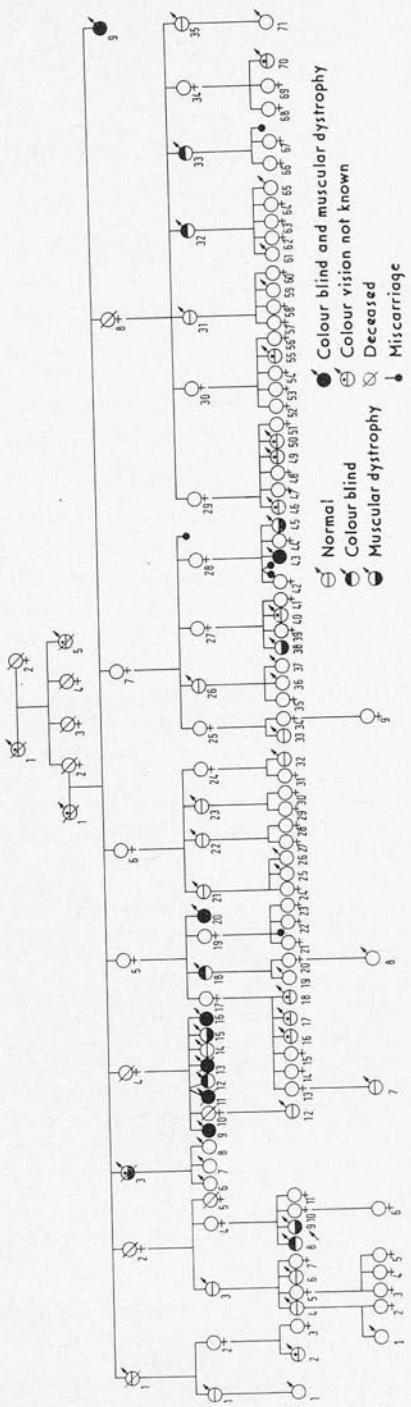

FIG. 1. Pedigree of family H.G. 588 (E).

The families

Family H.G. 588 (E). This family has been described in detail in a previous study (Emery *et al*, 1968/1969). The family has been restudied and extended. However no further cases (clinical or preclinical) have been identified and the pedigree information to date (Fig. 1) is essentially the same as previously described.

Family H.G. 153 (M). The pedigree of this family is shown in Fig. 2. Colour blindness appears to have occurred only in the offspring of III.11, although there are other males with muscular dystrophy in the family. Her father, II.3, suffered from muscular dystrophy, making her an obligatory carrier of this gene, but unfortunately nothing is known about his colour vision. V.21, V.31, and VI.2 were identified as preclinical cases of muscular dystrophy on the basis of serum creatine kinase estimations. V.17 and V.18 were suspected of being preclinical cases several years ago and have since developed obvious signs of the disease.

Linkage analysis

The lod scores for family E were recalculated, taking into account the additional individuals in the family and without classifying III.8 as a definite carrier. These changes reduced the previous lod scores somewhat. For family M, the origin of the deutan allele is unknown and so four possibilities—

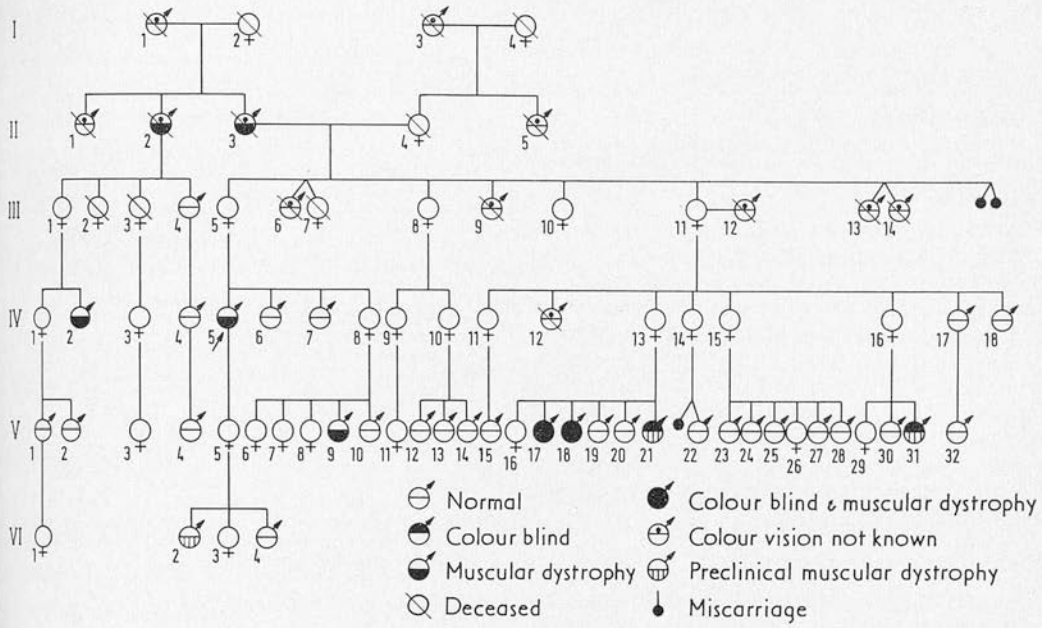

FIG. 2. Pedigree of family H.G. 153 (M).

TABLE I

BECKER-TYPE MUSCULAR DYSTROPHY AND DEUTAN COLOUR BLINDNESS; LOD SCORES AND ANTILOGS (RELATIVE LIKELIHOOD)

	Recombination Fraction (θ)								
	0·05	0·10	0·15	0·20	0·25	0·30	0·35	0·40	0·45
Family E									
Lod score	−2·94	−1·00	−0·08	0·41	0·64	0·69	0·62	0·45	0·23
Antilog	0·001	0·016	0·83	2·57	4·37	4·90	4·17	2·82	1·70
Family M									
Lod score	0·39	0·83	0·90	0·80	0·61	0·37	0·14	−0·01	−0·06
Antilog	2·46	6·76	7·94	6·31	4·07	2·34	1·38	0·98	0·87
Sum of scores									
Lod scores	−2·55	−0·17	0·82	1·21	1·25	1·06	0·76	0·44	0·17
Antilog	0·003	0·676	6·61	16·22	17·78	11·48	5·75	2·75	1·48

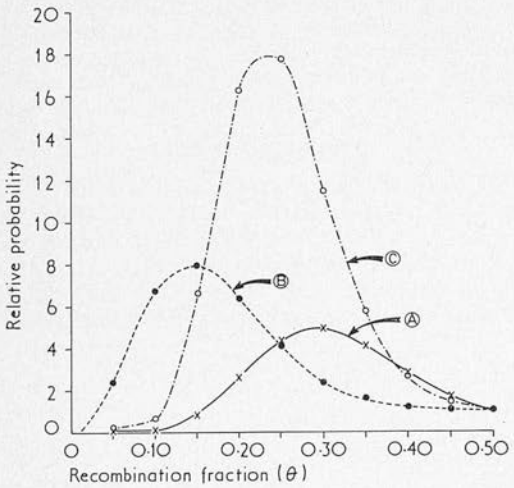

FIG. 3. Relative probabilities of linkage for various values of the recombination fraction for Becker muscular dystrophy and deutan-type colour blindness. **A:** family E; **B:** family M; **C:** families E and M combined.

(1) from II.3, (2) from II.4, (3) from III.12, and (4) mutation in III.11—were considered. It turned out that (1) was by far the most important in determining the lod scores which are given in Table I. The combined results indicate that the maximum likelihood estimate of the recombination fraction is 0·23 (Fig. 3) with 95% confidence limits of 0·13 to 0·43. The probability of the loci for Becker muscular dystrophy and deutan colour blindness being within measurable distance of each other is roughly 7:1.

Discussion

The results of the present study confirm that the loci for Becker type muscular dystrophy and deutan colour blindness are within measurable distance of each other. Since this is not true for Duchenne muscular dystrophy and colour blindness it seems that Becker and Duchenne muscular dystrophy, though both X-linked are not allelic.

In the previous study of Becker muscular dystrophy and deutan colour blindness (Emery *et al*, 1968/1969) the estimate of the recombination fraction was 0·28 with 95% confidence limits of 0·15 to 0·50, and the odds on linkage was about 4:1. With the additional material presented here, the estimate becomes rather lower (0·23) with narrower confidence limits (0·13 to 0·43 and the odds on linkage now slightly greater (7:1).

Grateful thanks are due to Mrs E. R. Clack for her invaluable help in tracing families.

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Recurrence risks from family history and metric traits

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The threshold model of disease liability (Falconer, 1965) has proved a useful tool for summarizing and comparing familial frequencies for diseases and conditions not inherited in a simple Mendelian manner. The model also provides a basis for estimating recurrence risks for specific family histories, given the population frequency of the condition and the correlation in liability between relatives (Smith, 1971; Curnow, 1972; Mendell & Elston, 1974). These methods use information only on the disease status of family members. Often there is additional information on items or traits associated with the condition and this could be included so as to improve the estimate of the recurrence risk in a specific family. The object of this paper is to derive methods which can utilize information on metric traits associated with a familial condition. For example, blood pressure in hypertension or blood glucose levels in diabetes are informative in estimating risks for these diseases. The usefulness of such information in practice will be examined, studying the size of possible changes in the estimates of risk and the increases in accuracy of the risk estimates obtained.

PRINCIPLES

Details on disease status of relatives are limited in value because individuals are classed either normal or affected (or intermediate, Reich, James & Morris, 1972). Thus rather than knowing the specific liability to the disease for each individual, only the mean liability of the group can be assigned. This coarse grouping does not introduce any bias into the estimation of recurrence risks, but rather it gives estimates of liability which are poorly correlated with the true liability of the individual at risk. In statistical terms the estimates are approximately unbiased but they are not efficient in that the residual variation in the estimate of liability is still high. In biological terms, the risk estimate is an average and includes individuals with a wide range of true risks and so its value for any particular case is decreased. Further information may help to reduce the residual variation in the risk estimate and so allow more accurate risks to be given for a specific family.

The kind of additional information considered here is that given by a metric or continuous trait associated with the condition. The metric trait may vary in the form of its association with liability for the condition. It may serve to define the disease, such as blood glucose levels in diabetes, and so measure liability directly. Or it may be correlated with liability either because it is a factor in the cause of the disease or because it is a result of the disease. The measured (phenotypic) correlation of the metric trait with liability may be due either to genetic effects or to non-genetic ('environmental') effects or to a combination of both. By definition, it is assumed that the risk of the disease is entirely dependent on the liability of the individual and the related trait is merely one of the factors determining liability.

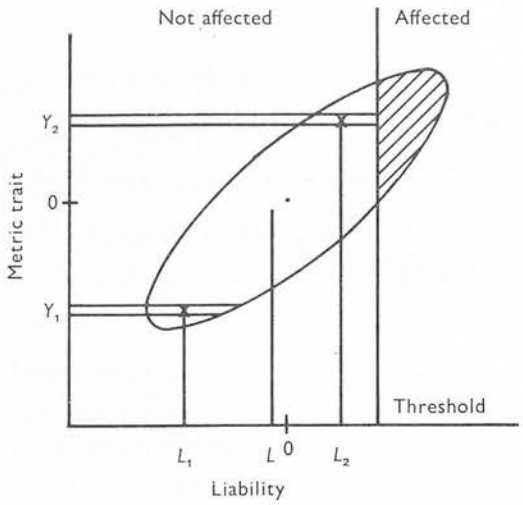

Fig. 1. Diagram showing the mean liabilities of unaffected individuals, L_1 given Y_1, L_2 given Y_2 and L for the average of all unaffected.

The nature of the information provided by the metric trait is illustrated in Fig. 1. The mean liability of unaffected individuals is L. With information on the correlated metric trait, the mean liabilities of unaffected individuals with trait values Y_1 and Y_2 are L_1 and L_2 respectively. Thus some differentiation among unaffected individuals may be achieved. The higher the correlation between liability and the trait, the greater will be the amount of information the trait can provide about liability and risks.

Continuous metric traits are already widely used in medicine as diagnostic indications of many familial and non-familial disorders. The aim is usually to detect abnormal function which may be diagnostic of the disease; that is, to detect individuals with abnormal levels for the trait. If the disease causes individuals to be no longer part of the normal distribution for the trait in the population, then trait information on such individuals cannot be used by the present methods. The emphasis here is less on abnormality for the trait but rather on unaffected individuals whose trait values lie within the normal range but which are raised because of the association with liability to the familial disease.

METHOD

The method used is an extension of an approximate method given by Mendell & Elston (1974) to derive recurrence risks for a given family history. The solution depends on formulae by Aitken (1934) for the variances and covariances of a multivariate normal distribution after selection of one of the variables. The procedure can then be applied in turn to further variables. Aitken's formulae depend on the assumption that the selected variable still has a normal distribution after selection. This will not be true with the threshold model where selection is by truncation. The approximation introduced by Mendell and Elston was to consider the truncated distribution as normal. They showed that, in estimating recurrence risks in families, the approximation gave quite accurate results. In the present paper the accuracy of the approximation has been assessed by comparing the results with some exact results derived by Curnow (1974).

The associations among relatives for the liability (L) to a disease and for a metric trait (Y) can be represented by a symmetric variance–covariance matrix V. For simplicity consider both

Table 1. *Symmetric variance – covariance matrix of liability and a metric trait (see text)*

	Liability		Metric trait			Liability
	L_1	L_2	Y_1	Y_2	Y_I	L_I
Variable	1	2	3	4	5	6
$V =$	V_{11}	V_{12}	V_{13}	V_{14}	V_{15}	V_{16}
		V_{22}	V_{23}	V_{24}	V_{25}	V_{26}
			V_{33}	V_{34}	V_{35}	V_{36}
				V_{44}	V_{45}	V_{46}
					V_{55}	V_{56}
						V_{66}

ts of variables as standardized; that is, expressed with a mean of zero and a variance of unity ($V_{ii} = 1$). Consider the matrix V for two relatives (1 and 2) and an individual (I) whose risk is be estimated. V can be arranged in a form convenient for reduction by the Aitken procedure, in Table 1. V_{ii} and V_{ij} are respectively the variance for variable (i) and the covariance for iables i and j. The correlation between any pair (i, j) is then

$$r_{ij} = V_{ij}/\sqrt{(V_{ii} . V_{jj})}.$$

suming a multi-normal distribution the Aitken procedure can be used to reduce the matrix to allow for the disease status of the first relative. Thus the residual variances and covariances en that relative 1 is affected are approximately

$$V_{ij.1} = V_{ij} - V_{1i}V_{1j}a_1\,(a_1 - x_1)/V_{11},$$

ere a_1 is the mean liability for affected individuals and x_1 is the threshold value. The residual relations are then

$$\mathrm{r}_{ij.1} = \mathrm{V}_{ij.1}/\sqrt{(\mathrm{V}_{ii.1}\mathrm{V}_{jj.1})}$$

l the adjusted threshold value for relative (i) is given by

$$\mathrm{x}_{i.1} = (\mathrm{x}_i - \mathrm{b}_{i1}\mathrm{a}_1)\sqrt{(1 - \mathrm{r}_{i1}^2\mathrm{a}_1\,(\mathrm{a}_1 - \mathrm{x}_1))},$$

ere b_{i1} is V_{i1}/V_{11}, the regression of variable i on 1. The quantity $a_{i.1}$ can be easily derived from normal curve given $x_{i.1}$.

The same procedure can be repeated for the disease status of relative 2, and then for further tives in turn, thus

$$V_{ij.12} = V_{ij.1} - V_{i2.1}V_{j2.1}a_{2.1}\,(a_{2.1} - x_{2.1})/V_{22.1}.$$

he relative is not affected then a_i is replaced by $-a_iF_P(1 - F_P)$, where F_P is the population quency of the condition.

The reduced matrix in the example is now $V_{.12}$:

$$\mathrm{V}_{.12} = \begin{pmatrix} V_{33.12} & V_{34.12} & V_{35.12} & V_{36.12} \\ & V_{44.12} & V_{45.12} & V_{46.12} \\ & & V_{55.12} & V_{56.12} \\ & & & V_{66.12} \end{pmatrix}$$

has the form of a set of multiple regression equations for variables 3, 4 and 5 on variable 6. ing yields the partial regression coefficients. For example, $b'_{63.12}$ is the regression of the in- dual's liability (variable 6) on variable 3, taking the other variables (4 and 5) into account.

In the reduced matrix ($V_{.12}$) above the term $V_{66.12}$ is the residual variance in the individual's liability after allowing for the disease status of his relatives (variables 1 and 2). Information on the metric trait for the individual and for his relatives will account for further variation. This further reduction in variance due to regression on variables 3, 4 and 5 is

$$V_{\text{reg}} = \sum_{i=3}^{5} b'_{6i.12}\, V_{6i.12}.$$

The residual variance in the individual's estimated liability (variable 6) after allowing for all the other variables is thus

$$V_R = V_{66.12} - V_{\text{reg}}.$$

This indicates how precise the estimate of liability is and allows a confidence interval to be set. The total variation in liability accounted for is ($1-V_R$) and this is the square of the multiple correlation between the estimate and the true liability.

The liability of the individual at risk can now be estimated as follows:

$$L_I = \frac{1}{\sqrt{V_R}} \left\{ x_6 - a_1 V_{61}/\sqrt{(V_{11})} - a_{2.1} V_{62.1}/\sqrt{(V_{22.1})} - \sum_{i=3}^{5} b'_{6i.12} \left[Y_i - a_1 V_{i1}/\sqrt{(V_{11})} - a_{2.1}\, V_{i2.1}/\sqrt{(V_{22.1})} \right] \right\}.$$

This takes account of the residual variation (V_R), then adjusts the individual's threshold value (x) for the disease status first of relative 1, then of relative 2 given relative 1. Similarly the trait value for each relative is adjusted before weighting the information by the appropriate partial regression coefficient in the equation.

The procedure can be extended in principle to any number of relatives of any degree of relationship. However, as more relatives are included the matrix becomes large. Errors arising from the approximation in using the Aitken procedure may also accumulate. However, details on a trait on close relatives may make the inclusion of more distant relatives unnecessary. Note again that the derivation and theory depend on phenotypic observed effects and require no genetic interpretation of the parameters.

The methods have been programmed for sibships with two parents and up to four sibs. The program reads in or generates the matrix V, reads an array giving the family history and measurements on the trait. It then proceeds through the methods outlined above, allowing for print-out checks at each stage, and finally printing the estimated liability, risk and variance explained. The program (RISKCT) is available on request.

Correlation estimates

To apply the above methods for deriving recurrence risks, estimates of the variances and covariances among the traits are required. All the variables are standardised to have zero mean and unit variances and the covariances then are the correlations among the variables. In matrix V these are the phenotypic correlations for all combinations of liability and metric trait among the various relatives. The correlation in liability between relatives is estimated from the frequency of the disease in the population (F_P) and the frequency in relatives of affected individuals (F_R) (Smith, 1970; Mendell & Elston, 1974). The correlations among relatives for the metric trait can be measured directly from samples of relatives. The correlations between the metric trait and liability can be estimated as the difference in the trait between relatives of unaffected and of

ffected individuals, divided by the difference between the average liabilities of unaffected and f affected individuals. If being affected precludes or affects the measurement of the metric rait, then only unaffected individuals can be measured. The mean value for those who become ffected at some later date, compared with those still unaffected, can be used to derive a rrelation estimate.

RESULTS

In this section we are concerned mainly with three aspects of the method. The first is to assess he accuracy of the approximation in risk estimation with trait information. The others concern he value of including information on a metric trait and the magnitude of changes in risks rought about by trait information.

ccuracy

Mendell & Elston (1974) compared recurrence risks derived by the Aitken procedure using their pproximation with the exact risks (Curnow, 1972; Smith, 1971). They found very good agreeent, with errors usually less than 1 % of the true risk and never larger than 5 % of the true sks. The same result was found here on including information on a correlated trait and comring the risks with those derived by Curnow (1974). These were for a range of population equencies and correlation matrices but dealt only with one relative and the individual at risk. he accuracy of the method when several relatives are included cannot be assessed until the act risks are known. These would require the numerical integration of multiple integrals.

ariation explained

A guide to the value of different pieces of information in estimating risks can be got by compar- their effects individually. This value can be gauged through the correlation of the estimated bility and the true liability for the individual whose risk is being estimated. The proportion of variation in liability explained is then simply the square of the correlation coefficient. This hown in Figure 2 for a range of correlations with liability and for first-degree relatives. The it can apply directly to the individual at risk and so can account for a greater proportion of variation in liability than other information which is indirect, being through a relative. s if there is trait correlated with liability it will usually be very worth while including it in risk estimation. The other graphs in Fig. 2 assume that the correlations for relatives are portional to the degree of relationship. Then the variation in liability explained by the affected atives and by the trait on a relative is similar for the same level of correlation. However, the rmation from unaffected relatives is much less useful especially if the disease is very rare. f there is more than one piece of information used to estimate risk, the total variation ounted for is, of course, not the sum of the separate effects, since these are likely to be elated. It is, however, derived directly in the matrix calculations as described in the methods ion. There are two aspects of interest; the total variance accounted for and the increase in proportion accounted for by the addition of each piece of information. A series of results is n in Table 2. To reduce the number of combinations of phenotypic correlations in the V rix, the examples are presented in genetic rather than in phenotypic terms. Consider two s, high (·0) and low (·05), respectively for the heritability of liability (h_L^2), for the herita- of the trait (h_T^2) and for the genetic correlation (r_G) between liability and the trait.The us correlations in matrix V can then be derived using a strictly genetic interpretation, as

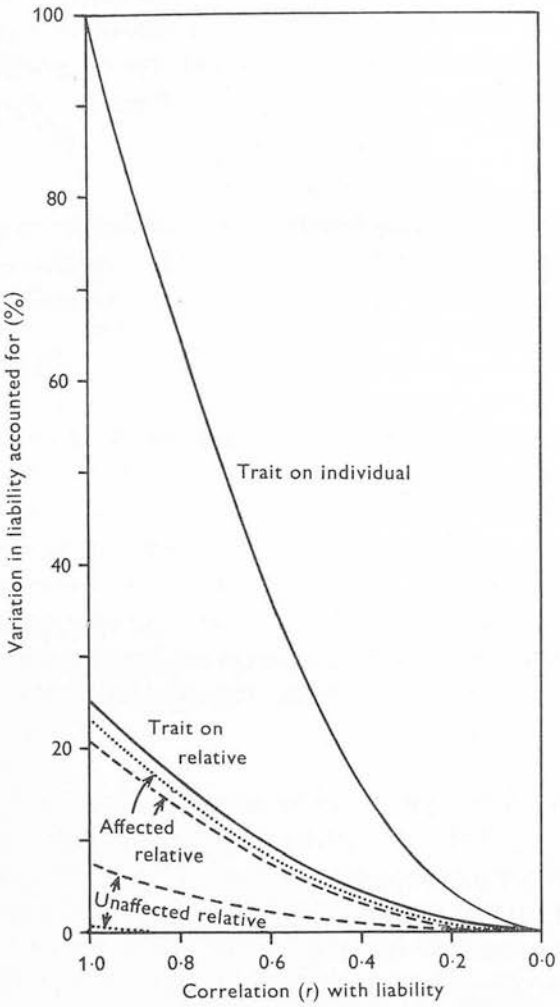

Fig. 2. Variation in liability accounted for by separate pieces of information on a correlated metric trait and on disease in a relative. ———, Trait. Disease: - - - - -, 10 %; ....., 0·1 %.

shown in Table 2. For example, the correlation in liability between first-degree relatives V_{12}, V_{16}, V_{26}, is $(\frac{1}{2})h_L^2$ and the correlation between liability and the trait V_{13}, V_{24}, V_{56}, is given by $r_G h_L h_Y$.

In Table 2 the variance accounted for is similar for different frequencies of the disease showing that the population frequency has a relatively minor effect on the amount of variation explained. As already noted, unaffected relatives contribute less information at low frequencies than at high frequencies. The amount of variation explained in any situation depends greatly on the correlation between the trait and liability, as would be expected. As the correlation increases, the value of the information on the trait also increases. If the correlation is unity, then of course all the variation in liability can be accounted for, since the trait gives a direct measure of liability for the individual at risk (Curnow, 1974). The additional pieces of information add progressively to the variation accounted for and the total may be 5–10 times the percentage originally accounted for by one affected relative. Additional relatives add further to the variation accounted for,

Table 2. *Percentage of variation in liability accounted for by different combinations of information, and for a range of genetic parameters and population frequencies*

						Information on:						
Family history												
Affected first degree relative						1	1	1	—	1	1	1
Unaffected first degree relatives						—	2	2	—	—	2	2
Trait												
On unaffected first degree relatives						—	—	2	—	—	—	2
On the individual at risk						—	—	—	1	1	1	1
Population frequency (%)	Heritability of liability h_L^2	Correlation between relatives $(\frac{1}{2})h_L^2$	Heritability of the trait, h_X^2	Genetic correlation r_G	Phenotypic correlation, $r_G h_L h_X$	Percentage of variation in liability accounted for:						
10	0·5	0·25	0·5	0·5	0·25	5·4	8·4	9·6	6·2	10·3	12·8	13·1
			1·0	0·5	0·35	5·4	8·4	10·6	12·5	15·5	17·4	17·6
			0·5	1·0	0·50	5·4	8·4	14·1	25·0	26·4	27·3	29·1
			1·0	1·0	0·71	5·4	8·4	19·3	50·0	50·0	50·0	50·0
	1·0	0·50	0·5	0·5	0·35	20·7	21·3	22·5	12·5	28·8	37·4	37·7
			1·0	0·5	0·50	20·7	21·3	34·8	25·0	37·3	44·1	45·4
			0·5	1·0	0·71	20·7	21·3	37·2	50·0	55·8	59·3	61·5
			1·0	1·0	1·00	20·7	21·3	46·1	100·0	100·0	100·0	100·0
0·1	0·5	0·25	0·5	0·5	0·25	5·8	6·1	8·0	6·2	10·7	11·0	11·5
			1·0	0·5	0·35	5·8	6·1	9·4	12·5	15·9	16·0	16·2
			0·5	1·0	0·50	5·8	6·1	13·8	25·0	26·5	26·5	29·1
			1·0	1·0	0·71	5·8	6·1	19·6	50·0	50·0	50·0	50·0
	1·0	0·50	0·5	0·5	0·35	23·0	25·1	27·9	12·5	30·7	32·3	33·4
			1·0	0·5	0·50	23·0	25·1	30·5	25·0	38·7	40·1	41·2
			0·5	1·0	0·71	23·0	25·1	37·0	50·0	56·5	57·2	61·3
			1·0	1·0	1·00	23·0	25·1	48·1	100·0	100·0	100·0	100·0

but at a decreasing rate. For example, if the trait is measured on the individual at risk, information on the trait in relatives does not account for much additional variation. Some compromise on the effort of collecting the information and its value will thus be sought. Finally, in Table 2, except in the extreme situations with very high correlations, there is usually a substantial amount of the variation in liability left unexplained. That is, the residual variation about the risk estimate is still large, so that the risk estimates are not very precise and there is still plenty of scope to improve their accuracy further.

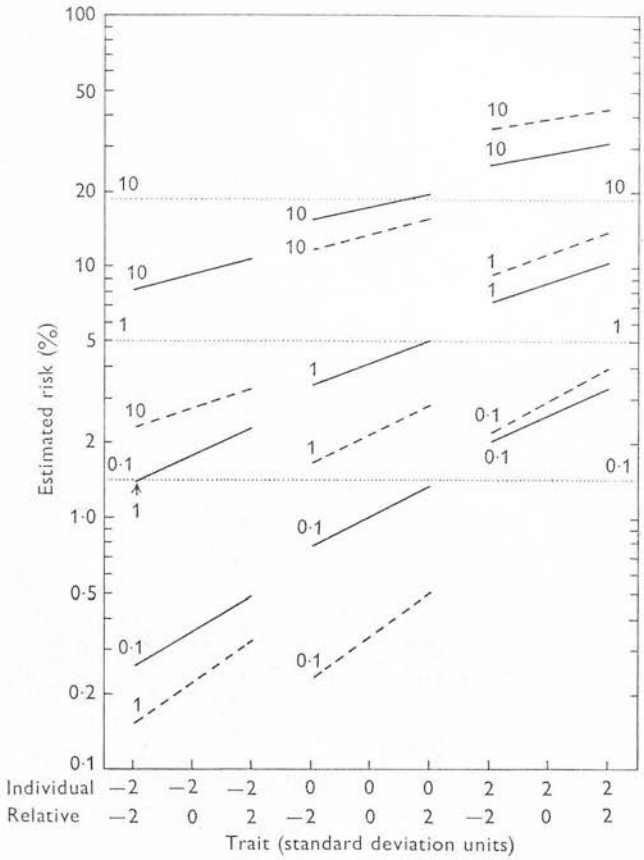

Fig. 3. Recurrence risks for an individual with an affected first-degree relative and for a range of values for a metric trait in the individual and in an unaffected first-degree relative. The horizontal dotted lines are the empiric risks (heritability = 0·6) for three levels of population frequency 10 %, 1 %, and 0·1 %. The correlations between the metric trait and liability are 0·21 (solid lines) and 0·42 (dashed lines) respectively.

Risk estimates

Additional information on a trait may also change the value of the risk estimate appreciably. Thus the risk will be specific to a family with a given set of information, rather than being an average and applying to all families at risk. A series of examples is given in Fig. 3. Again, for simplicity, the correlations in the matrix V are derived directly from a set of genetic parameters. The examples deal with a heritability of liability (h^2_L) of 60 % and three population frequencies, 10 %, 1 % and 0·1 %. These should represent a wide range of familial conditions in man. For the metric trait, heritabilities of 30 % and 60 % were chosen, and genetic correlations with liability

of 0·5 and 0·7 respectively. The phenotypic correlations ($r_G h_L h_T$) of the trait and liability are thus 0·21 and 0·42 respectively. The risks are given for individuals with one affected first degree relative (dotted lines) and also with information on a trait for the individual at risk and for an unaffected relative, each with possible values -2, 0 and $+2$ standard deviation units from the mean. The variance explained by one affected relative was 9 % and this was increased to 13 % and to 23 % for the correlations 0·21 and 0·42 respectively by the additional information.

In Fig. 3 the risks may be greatly modified by including a correlated metric trait, especially when the correlation between the trait and liability is high. As before, the trait measured on the individual at risk is much more important than the trait in a relative, but the latter does contribute to the estimate of risk. Individuals with high values for the trait may have double the average risk, while in those with low trait values the risks may be halved or even reduced to 10 % or one % of the original empiric risk. The higher the correlation with liability, of course, the greater the increase in risk for individuals with high values of the trait, and the lower the risk with low trait values. Measurements on one unaffected relative alter the risk estimates less but if several unaffected relatives were included, collectively they could have a greater effect.

Example

To illustrate the use of the method consider an individual with a family history of simple glaucoma; with an affected father and an affected sib, but with a normal mother and two normal sibs. The frequency of glaucoma among persons over 40 is about 1 % (Bankes *et al.* 1968). In first-degree relatives of cases the frequency is about 4–5 % (Leighton, 1968). This gives a correlation of 0·25 between first-degree relatives for liability to glaucoma. Ignoring age effects, the estimated risk to a sib given the above family history is about 9 % and some 10 % of the variation in liability is accounted for.

A raised intra-ocular pressure (IOP) is characteristic of most patients with simple glaucoma, but not all individuals with raised IOP (over 21 Hg) have glaucoma (Bankes *et al.* 1968). Armaly, Monstavicius & Sayegh (1968) found that IOP (standardized for sex and age) was raised (0·156) in relatives of patients with glaucoma compared with ($-0·283$) in relatives of normal controls. The regression (and correlation) of IOP in relatives on liability of cases (2·665) and of controls ($-0·026$) is estimated as

$$b = r = \frac{0·156-(-0·283)}{2·665-(-0·026)} = 0·16.$$

No estimates of the correlation between IOP and liability in the same individual seem available and so an arbitrary value of 0·4 was used. The correlation in IOP among first degree relatives is about 0·3 (Armaly *et al.* 1968).

The results from using different kinds of information from the family are given in Table 3. As either information on family history or on IOP levels in the family is added, the variation explained increases. The risk depends largely on the individual's own IOP and this is moderated only slightly by the IOP levels in relatives.

DISCUSSION

In practice the problems of estimating recurrence risks are likely to be biological rather than mathematical. The mathematical methods described here are versatile and appear to provide good approximations to theoretical risks, given multi-variate normal distributions and good

Table 3. *An example of estimated risks and variation in liability accounted for by using different kinds of information on family history of glaucoma and on intra-ocular pressure (IOP) in relatives*

Information used	Variation accounted for (%)	Risk (percent): Individual's IOP (s.d. units)			
		—	2	0	−2
Positive family history	9·0	9·7	—	—	—
Full family history	10·0	8·8	—	—	—
Individual's own IOP	16·0	—	4·8	0·6	0·1
Positive family history plus individual's own IOP	21·2	—	19·1	4·7	0·7
Full family history plus individual's own IOP	21·8	—	17·8	4·3	0·6
Full family history Plus individual's own IOP plus IOP on unaffected relatives (average)					
+2	21·9		18·6	4·7	0·7
0	21·9		17·5	4·3	0·6
−2	21·9		16·4	4·0	0·6

estimates of the basic parameters. The main query in their application will be whether the theoretical distributions are appropriate in describing the actual joint distribution of liability and the trait. However, if the distributions are continuous, and can be transformed to quasi-normality, then the mathematical methods seem to be quite robust and may be appropriate for estimating recurrence risks.

An advantage of the methods is that they can deal with familial effects whether they are genetic or non-genetic or, as is likely, some combination of the two. The methods deal with correlations between relatives, whatever may be the cause of the correlation. Thus there need be no genetic interpretation of familial frequencies or correlated traits in the estimation of recurrence risks. If information is available on several traits they can all be included in estimating risks, simply by increasing the matrix to include them. To do this the correlations among the different traits, as well as with liability, would be required.

The method of estimating the recurrence risks depends on multiple regression maximising the multiple correlation of all the information available with the liability of the individual at risk. If the separate correlations are in error or are poorly estimated then the estimates of the risk and variance explained will be affected and may be misleading. It is thus important to derive as accurate estimates as possible for the correlations. It has proved surprisingly difficult to get from the literature reliable estimates of the correlations for many of the common familial disorders and associated metric traits. However, as outlined earlier, it should be readily possible to estimate them by collecting special sets of family material. A list of familial conditions with possible traits which might be useful in estimating risks is given in Table 4. Unfortunately, none of the congenital abnormalities seem to have metric traits with which they are correlated.

There is a paradox in the use of a correlated trait to supplement family history in estimating risks. If the correlation with liability is low then the trait adds little information. If the correlation is high then the individual's own value for the trait gives a good estimate of risk and largely supplants the family history and details on relatives. Thus it is when the correlation between trait and liability is intermediate, or when the individual at risk cannot be measured for example if he is too young or not yet born, that the methods here will be of most value.

If the distributions of the trait or of liability are discontinuous then the methods here may

Table 4. *List of familial conditions with correlated metric traits which may be useful in risk estimation*

Condition	Trait
Hypertensive heart disease	Diastolic blood pressure
Diabetes mellitus	Glucose tolerance test
Glaucoma	Intraocular pressure
Mental retardation	Intelligence quotient
Coronary heart disease	Lipoproteins
Schizophrenia	Personality scores
Gout	Uric acid
Epilepsy	E.E.G. measurements
Rheumatoid arthritis	Radiographic scores
Hypothyroidism	Protein-bound iodine
Allergy	Skin sensitivity tests.

invalid. When the discontinuity arises because the trait can be classed into only two classes, Aitken procedure for reducing the matrix can be applied to the trait as well as to liability. wever, with only two classes, the amount of information added is likely to be small. Alternaly if the trait can be graded into a number of classes, then these may be considered as serial ses in a normal distribution. When the discontinuities are associated with identifiable ndelian phenotypes, other methods of risk estimation should be used. For example, Heuch & 1972) have shown how to combine information on a metric trait, as well as other factors, in mating risks for Mendelian disorders. To deal with complex situations and multigeneration grees they have developed a general program PEDIG to estimate recurrence risks for any ily history.

or familial conditions which are heterogeneous, the correlation of one trait with a mixed ribution of liability is not likely to be high. Resolution of the heterogeneity may increase correlation for one subgroup and allow the trait to become a better indicator of those at for that group. For example, the resolution of coronary heart disease to forms with high m cholesterol or high triglyceride or high for both lipoproteins would allow better risk lictions to be made in relatives of cases and in individuals screened in the population.

SUMMARY

method for including information on an associated metric trait in the estimation of recure risks for familial conditions is presented. This depends on the correlations among relatives he trait, for liability to the condition and on the correlations between them. The values of family history, both positive and negative, and of measurements on the trait in the indivi- at risk and in his relatives are compared and expressed as the variation in liability accounted An example of the use of the method is given for measurements of intraocular pressure in coma.

tails on an associated trait can add considerably to the accuracy of the recurrence risk ates and can modify substantially the estimate of risk in the individual concerned.

thank Professor R. H. Curnow for allowing us to use his exact results with which to compare the imation made in this paper, and for constructive discussion and criticism throughout the work.

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Effects of Various Medical and Social Practices on the Frequency of Genetic Disorders

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INTRODUCTION

In the past many workers have studied the effects of various factors on the human gene pool [1–4]. The emphasis has usually been on single factors with dysgenic (deleterious) effects and on the long-term changes and time to reach new equilibria. However, short-term changes and the combined effects of several factors are of more interest and practical importance. In recent years a number of new medical practices, such as improved treatments for affected individuals, genetic counseling, and population screening, and social customs, such as family limitation or selective abortion, have been introduced and are being widely adopted. Not all of these are dysgenic, and some have eugenic (beneficial) effects on the gene pool. In this paper we will study the effects of a variety of such practices and the net effect of their combination and use in practice.

Scope of Study

We shall restrict the study largely to disorders with simple Mendelian modes of inheritance: autosomal recessive, autosomal dominant, and X-linked recessive. For autosomal recessive disorders it will be assumed that there is no heterozygote advantage. However, results have also been derived [5] for disorders with heterozygote advantage and for multifactorial disorders; these will be discussed briefly.

Long-term gene frequency changes giving new equilibria are mainly of theoretical interest. It is unlikely that they would be realized in practice since medical and social practices continually change. Similarly, rather than a single practice acting in isolation, it is more likely that several practices will operate simultaneously. For these reasons we consider short-term (single generation) changes in disease incidence and gene frequency for each factor studied. Then we can study the relative importance of the different factors on a common basis and go on to examine the net effect of several factors acting in combination, as likely in practice.

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Current Factors

There will always be many factors, some known but many unknown, acting on the gene pool. In practice it is often difficult to measure their effects or even to determine if any effects exist. Changes in gene frequency may result from mutation, migration, selection, or random drift. Here we are not concerned with the array of factors already acting on the gene pool. Rather we will restrict our attention to various new practices being adopted or proposed as a result of medical progress and social change. Thus no attempt will be made to measure the absolute change in disease incidence or gene frequency. Instead we consider only the net change brought about by a particular new factor or by a group of factors acting in combination.

NEW PRACTICES AFFECTING GENE POOL

The new factors considered are some practices which are being adopted or proposed at present for the prevention of genetic disease. They may be grouped roughly into those whose effects are largely dysgenic (1–3) and those with principally eugenic effects (4–7).

1. *Improved treatment of affected individuals.* With improved methods of detection and treatment, individuals with certain genetic disorders may survive longer and their reproductive fitness may be improved.

2. *Selection of mates.* For autosomal recessive conditions, heterozygous (Aa) carriers may select a mate who is homozygous normal (AA) and so avoid having affected (aa) offspring.

3. *Selective abortion with full reproductive compensation.* With selective abortion, affected offspring can be avoided and replaced by normal offspring to give the intended family size.

4. *Family limitation by all carriers.* In autosomal recessive conditions heterozygous (Aa) carriers may reduce or limit their family size because of their carrier state. This may be due to unwarranted concern about the risk to their offspring or to their difficulty in finding a homozygous normal (AA) mate.

5. *Family limitation by detected carriers at risk.* Where there is a risk to offspring, detected carriers for autosomal dominant and X-linked recessive disorders as well as detected $Aa \times Aa$ couples for autosomal recessive disorders may have no children or may limit their family size because of the risks.

6. *Artificial insemination in matings at risk.* In autosomal recessive disorders and in autosomal dominant and X-linked recessive disorders where the male is affected, artificial insemination by selected donors may be used to avoid having affected offspring.

7. *Selective abortion without reproductive compensation.* This is similar to practice 3, but no further offspring are conceived to replace those selectively aborted, so that actual family size will be lower than intended family size. Practices 3 and 7 are kept separate for simplicity, but a full treatment is given elsewhere [6]. For X-linked recessive conditions three situations are considered, namely, the selective abortion of affected males, of all males, and of affected

males and carrier females. For autosomal dominant conditions with incomplete penetrance or late onset, prenatal diagnosis may also be incomplete, and a term can be included for this [5]. However, for simplicity, it is assumed here that all carriers (Aa) could be detected in utero.

The overall effects of these practices will depend both on the proportion adopting them and on the extent to which they are applied. They will also depend on whether the practice is adopted before (prospectively) or after (retrospectively) detection of an affected individual in the family. The changes in disease incidence and in gene frequency will always be smaller with retrospective detection than with prospective detection.

ASSUMPTIONS AND CONVENTIONS

For the three classes of disease considered, the change in disease incidence is taken to be the difference between that in the offspring generation at birth and that in the parental generation at birth. The change (Δ_1) which results from natural selection alone is subtracted from the change (Δ_2) which results from a particular practice together with natural selection to obtain the net change ($\Delta_2 - \Delta_1$) due to the practice.

For gene frequency changes, the change will be measured as the difference between the frequency in parents at reproduction and the frequency in offspring at reproduction. This is because for some practices (e.g., selective abortion with reproductive compensation) the gene frequency in offspring born does not reflect the change in their genotype distribution, which determines the number of deleterious genes passed on to the next generation. This problem can be avoided by considering the gene frequencies at reproduction instead of at birth.

In many previous studies it has been assumed that current forces acting on the gene pool are in approximate equilibrium. This is unlikely in developed societies where survival and selection parameters have been radically altered recently and are continually being modified. Here no assumptions about initial equilibria are required. Rather we consider the *net* effect of applying the practice, assuming all the other factors remain unchanged.

A summary of the variables required and symbols used is given in table 1. The symbol d combines several factors which may be considered separately to show their individual effects [5]. Suppose for a certain genotype (or mating type) a proportion w is detected, and, of these, a proportion c adopts the practice being considered. They apply it to an average extent f. Then $d = wcf$ measures the average extent to which the practice is applied by *all* of the particular genotype or mating type being considered.

Other variables for factors complicating the changes in disease and gene frequency can be included. If detection is retrospective rather than prospective, the changes are usually P_r times those for prospective detection, where P_r is the proportion of offspring born after detection of the disorder in the family. For a family of size n and a recurrence risk of x, the proportion of offspring born after detection

TABLE 1

VARIABLES AND SYMBOLS USED

Variable	Symbol
Frequency of normal allele	p
Frequency of deleterious allele	q
Dominant allele	A
Recessive allele	a
Mutation rate to the deleterious allele	μ
Penetrance of A (or proportion of A- manifesting before reproduction)	y
Coefficient of selection against individuals of genotype x	s_x
Change in s_x	Δs_x
Average extent to which practice is applied by *all* of particular genotype (or mating type) considered	d
Proportion of offspring born after *detection* of affected individual in family	P_r

is $1 - [1 - (1 - x)^n]/nx$ [7]. This expression can be combined with a theoretical family size distribution, such as the Poisson or the negative binomial, or used with the observed family size distribution to evaluate P_r. For example, using the distribution of completed family size in Britain from the 1961 census, P_r was .23 and .38 for $x = \frac{1}{4}$ and $x = \frac{1}{2}$, respectively [5].

For autosomal recessive and X-linked recessive diseases, manifestation is usually before reproductive age. For autosomal dominant diseases, a term y for incomplete penetrance or for the proportion of A- carriers manifesting the disease before reproductive age has been included, since these features are common for autosomal dominant conditions. Mutation has also been considered, but in most cases the terms cancel out of the expressions for net change. For X-linked recessive diseases the gene frequency is taken as $\frac{1}{3}(q_M) + \frac{2}{3}(q_F)$, where the subscripts M and F refer to male and female, but the changes are expressed in terms of q_F since it is less affected than q_M by the various practices.

METHOD

The methods used for calculating the changes in frequency are similar for the different practices and modes of inheritance. A complete set of calculations and formulas is given by Holloway [5]. Here a few examples are worked to illustrate the methods, and a summary of the results for all cases is given in table 2.

The simplest way to derive the net changes is to write the expression for the expected frequency with the factor acting and then to subtract from it the expression for the expected frequency omitting the factor under study. Many of the terms then cancel out and need not be evaluated. Two examples are given using this difference method, and a third example is included to show how the effects of the different variables may be evaluated separately and then combined to give the net change.

TABLE 2

APPROXIMATE NET CHANGES IN DISEASE INCIDENCE AND GENE FREQUENCY FOR VARIOUS PRACTICES AND MODES OF INHERITANCE

PRACTICE	AUTOSOMAL RECESSIVE		AUTOSOMAL DOMINANT		X-LINKED RECESSIVE	
	Disease Incidence (q^2)	Gene Frequency (q)	Disease Incidence ($2qy$)	Gene Frequency (q)	Disease Incidence in Males (q_F)	Gene Frequency (q_F)
Dysgenic practices:						
1. Improved treatment ...	$2q^3\Delta s_{aa}$	$q^2\Delta s_{aa}$	$2qy^2\Delta s_{A\cdot}$	$(\mu+q)y\Delta s_{A\cdot}$	0	$\frac{1}{3}(\mu+q_F)\Delta s_a$
2. Selection of mate	$-q^2d(2-d)$	$q^2s_{aa}d(2-d)$	...	...	...	...
3. Selective abortion with full reproductive compensation:						
a) Affected individuals ..	$-q^2d$	$q^2d(s_{aa}-\frac{2}{3})$	$-2qy^2d(1-s_{A\cdot})$	$-qyd(1-s_{A\cdot})$	$-q_Fd$	$\frac{1}{3}q_Fd(s_a-\frac{2}{3})$
b) All males*	...	...	...	...	$-q_Fd$	$\frac{1}{3}q_Fds_a$
c) Affected males and carrier females*	...	...	...	...	$-q_Fd$	$-\frac{1}{3}q_Fd(2-s_a)$
Eugenic practices:						
4. Family limitation by all carriers	$-q^2d(2-d)$	$-qd$	...	...	...	...
5. Family limitation by detected carriers at risk ...	$-q^2d$	$-q^2d(2-s_{aa})$	$-2qy^2d(1-s_{A\cdot})$	$-qyd(1-s_{A\cdot})$	$-q_Fd$	$-\frac{1}{3}q_Fd(2-s_a)$
6. Artificial insemination in matings at risk	$-q^2d$	$-q^2d(1-s_{aa})$	$-qy^2d(1-s_{A\cdot})$	$-\frac{1}{2}qyd(1-s_{A\cdot})$	0	$-\frac{1}{3}(\mu+q_F)d(1-s_a)$
7. Selective abortion without reproductive compensation:						
a) Affected individuals ..	$-q^2d$	$-q^2d(1-s_{aa})$	$-2qy^2d(1-s_{A\cdot})$	$-qyd(1-s_{A\cdot})$	$-q_Fd$	$-\frac{1}{3}q_Fd(1-s_a)$
b) All males*	...	...	...	...	$-q_Fd$	$-\frac{1}{3}q_Fd(1-s_a)$
c) Affected males and carrier females*	...	...	...	...	$-q_Fd$	$-\frac{1}{3}q_Fd(2-s_a)$

NOTE.—Symbols as in table 1.
* X-linked recessive disease.

Improved Treatment

For an autosomal recessive disorder, suppose an improved treatment allows the reproductive fitnesss of *aa* homozygotes to increase by $\Delta_{s_{aa}}$. The gene frequency in the next generation will then be

$$q_1 \simeq \frac{1}{2}(2pq) + q^2(1 - s_{aa} + \Delta s_{aa}) \simeq q - q^2(s_{aa} - \Delta s_{aa}).$$

The net change in gene frequency due to improved treatment is then

$$q_{1\,(\Delta s_{aa} \neq 0)} - q_{1\,(\Delta s_{aa} = 0)} \simeq q^2 \Delta s_{aa}.$$

Similarly the net change in disease incidence is

$$q_1{}^2{}_{(\Delta s_{aa} \neq 0)} - q_1{}^2{}_{(\Delta s_{aa} = 0)} \simeq 2q^3 \Delta s_{aa}.$$

Family Limitation by Carriers

If carriers of a deleterious X-linked recessive condition reduce their family size to an average extent d ($d = wcf$), the change in disease incidence is then directly $-q_F d$. The change in gene frequency is derived as shown in table 3. The net change

TABLE 3

FAMILY LIMITATION BY CARRIERS

GENERATION	STAGE	GENE FREQUENCY	
		Males	Females
0	Reproduction	q_M	q_F
1	Birth	$\mu + q_F(1-d)$	$\mu + \frac{1}{2}[q_M + q_F(1-d)]$
1	Reproduction	$[\mu + q_F(1-d)](1-s_a)$	$\mu + \frac{1}{2}[q_M + q_F(1-d)]$

NOTE.—X-linked recessive condition.

due to the practice is the change with $d \neq 0$ less the change with $d = 0$. This can be written directly and simplifies to $-\frac{1}{3}[q_F d(2 - s_a)]$, as in table 2.

Selective Abortion with Full Reproductive Compensation

As an example of the longer method of derivation, consider a more complex case. In an autosomal recessive disorder, suppose a proportion w of all $Aa \times Aa$ couples is detected prospectively and, of these, a proportion c practise selective abortion with full reproductive compensation. The situation for these matings (with $d = wcf$ and $f = 1$) is shown in table 4. The approximate incidence in offspring is then $q^2(1 - d)$, so the change in incidence between the parental and offspring generations is $-q^2 d$. (More accurately, the change is $-q^2 d + 2q^3 s_{aa}$, but the term for natural selection can be ignored if $d > 2qs_{aa}$, as is likely for rare severe autosomal recessive diseases.) Let q_1 be the gene frequency at reproduction

NOTE.—Symbols as in table 1.
* X-linked recessive disease.

in the parental generation. The gene frequency in offspring at conception is also q_1, and at reproduction this will be reduced by an amount $q_1^2 s_{aa}(1 - d)$ due to the loss of affected individuals born and by an amount $q_1^2 d$ due to selective abortion of affected fetuses. Both replace the normal loss of $s_{aa} q_1^2$ due to natural selection. To compensate for those aborted, an additional $q_1^2 d$ offspring are born, and two-thirds of these are heterozygotes. Putting these terms together, the net change in gene frequency due to the practice will be approximately

$$q_1^2[s_{aa} - s_{aa}(1 - d) - d + \frac{1}{2}(\frac{2}{3}d)] = q_1^2 d(s_{aa} - \frac{2}{3}).$$

RESULTS

In table 2, the changes expected often have a similar form so that some general results can be noted. By expressing the changes relative to the initial disease incidence or gene frequency, the relative changes can be made independent of the initial frequencies for most of the practices. The exception is for autosomal recessive conditions where the change in gene frequency usually depends on q^2 (and so is small) rather than on q. For autosomal dominant conditions the change in disease incidence is proportional to qy^2, where y is a measure of penetrance or of the proportion of carriers manifesting the condition before reproductive age. This is because the original disease incidence is qy and only a proportion y of carrier offspring will be affected. The change in gene frequency is usually $1/2y$ times the change in disease incidence. For X-linked recessive disorders the change in gene frequency is of the same order as the original disease incidence.

The apparent similarity of the formulas, however, may mask likely differences between the effects of the practices. These effects will depend on the extent to which the practice is adopted, which may vary widely. For example, in autosomal recessive conditions, only a small proportion of all carriers is likely to limit their family size (practice 4), while a much larger proportion of carriers known to be at risk (practice 5) may do so. Thus the term d may be quite different in magnitude for different practices.

In order to compare the relative sizes of the effects of the different practices for the different modes of inheritance, the changes expected are plotted in figure 1. The changes are expressed as a percentage of the original disease incidence or

TABLE 4

SELECTIVE ABORTION WITH REPRODUCTIVE COMPENSATION

PRACTICE	FREQUENCY	OFFSPRING BORN		
		AA	*Aa*	*aa*
Normal reproduction	$4p^2q^2(1 - d)$	1/4	1/2	1/4
Selective abortion	$4p^2q^2d$	1/3	2/3	0

NOTE.—Autosomal recessive disorder. $d = wcf$; $f = 1$.

gene frequency for varying levels of the extent (d) to which the practice is adopted by the particular genotype or mating type concerned. For autosomal dominant conditions with penetrance y, the extent of the practice becomes yd, since undetected heterozygotes cannot adopt the practice. The graphs represent a severely deleterious condition with $s = .9$, so there would initially be strong selection against affected individuals. For autosomal recessive disorders the percentage changes usually contain a term for gene frequency; $q = .02$ (as for cystic fibrosis in Caucasians) was chosen to represent these disorders.

The percentage changes are usually linear on the extent to which the practices are adopted, so the effects depend greatly on how much the practice is applied by the population considered. Improved fitness of affected individuals leads to

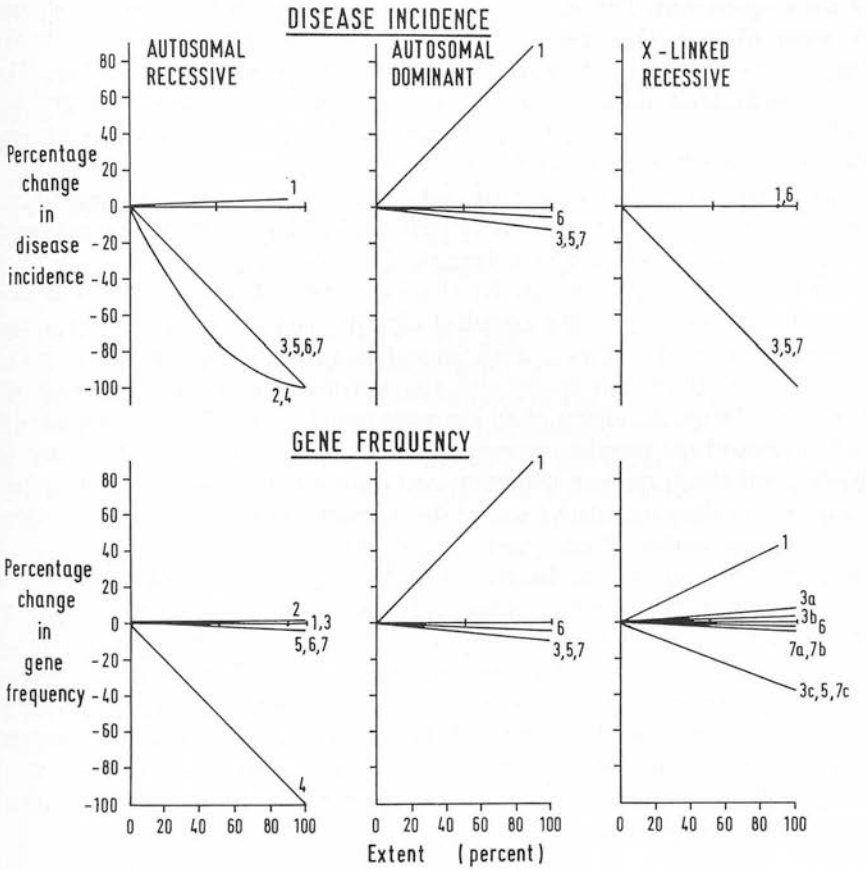

FIG. 1.—Percentage changes expected in disease incidence and gene frequency for different modes of inheritance, different practices, and varying extents to which practices are applied by particular genotypes or mating types. A severely deleterious condition is represented ($s = .9$); the autosomal recessive disease is assumed rare ($q = .02$). See table 2 for explanation of practices 1–7.

important increases in disease incidence for autosomal dominant conditions and in gene frequency for both these and X-linked recessive disorders, but has small effects on autosomal recessive conditions. The other practices can lead to large decreases in disease incidence for autosomal recessive and X-linked recessive conditions, but often have little effect on gene frequency. Thus their effects may be noncumulative and the practice would have to be reapplied each generation to benefit further from it. For example, in autosomal recessive disorders, either avoidance of carrier matings (practices 2 and 5) or selective abortion (practices 3 and 7) could temporarily eliminate the disorder from the population, but neither practice would have much effect on gene frequency. Thus they would have to be constantly reapplied or the disease incidence would revert to its original (or a higher) level. The graphs drawn, of course, depend on the values of s and q (.9 and .02, respectively), and the impressions may be different with different values of these parameters. For example, if $sy = .1$, as may be the case for late onset dominant diseases which have little effect on reproductive fitness (e.g., Huntington's chorea), the extent to which fitness can improve would be only 10%. However, if individuals who are possible carriers (because of their family history) limit their family size, the reductions in disease incidence and in gene frequency would be much larger than shown in figure 1.

One result stands out clearly for autosomal recessive disorders, namely, if a small proportion of *all* carriers limit their family size, there can be a large decrease in gene frequency. This is because the change depends on q, while all the other terms for autosomal recessive disorders (table 2) are proportional to q^2. Thus if detection alone or the attendant difficulty and concern of finding a homozygous normal mate causes a small proportion (1%–2%) of carriers to have no children or to limit their family size, the decrease in gene frequency incurred is likely to outweigh the effects of all the other practices. For X-linked recessive disorders most of the practices reduce disease incidence appreciably but have relatively small effects on gene frequency, and some are dysgenic. The main value of figure 1 is to show the relative size of the different possible effects for the different practices and modes of inheritance and to demonstrate again how some of the practices reduce disease incidence but may have dysgenic effects on the gene pool.

These results apply for prospective detection of genotypes (or matings) at risk. With retrospective detection the changes will be proportionately smaller depending on the stage of detection. For autosomal recessive and X-linked recessive disorders, changes will be less than 20%; for autosomal dominant disorders (with complete penetrance), the change will be less than 35% of that when detection is prospective. If the onset of the disorder is not early, many families may be completed before affected individuals are diagnosed, and a lower proportion of cases will be prevented.

Combination of Different Practices

Most of the practices considered are mutually exclusive; if individuals or couples adopt one, they cannot adopt the others. Thus their combined effect is

simply the sum of their individual effects. However, the effects of a change in fitness of affected individuals may be confounded with the other practices because the other practices may cause a reduction in the number of affected individuals. Hence, there are fewer individuals who can benefit from the treatment and fewer for natural selection to act against. The combined effect is then the sum of the changes resulting from the increase in fitness and from the other practices with the new value of fitness substituted. The latter changes are obtained by replacing s by the term $(s - \Delta s)$ in the formulas in table 2. For example, for autosomal recessive disorders the joint effect of increasing fitness and reducing the fitness of $Aa \times Aa$ couples would be to change the gene frequency by $q^2\Delta s_{aa} - q^2d[2 - (s_{aa} - \Delta s_{aa})]$.

Example

To illustrate the use and combination of the results derived above, consider the autosomal recessive disease sickle cell anemia in U.S. blacks. The incidence is about 25 per 10,000 ($q = .05$), and several programs devised to reduce its frequency have been proposed [8]. Carriers can be detected by screening, and antenatal diagnosis of affected homozygotes may also soon be possible. In the past, with the absence of heterozygote advantage in the United States and low fitness ($s \simeq 1.0$) of affected individuals, the disease incidence and gene frequency should have been slowly declining. Now with better medical diagnosis and care, the fitness of affected individuals has been increasing and may be as high as .3 ($s = .7$; [9]).

Suppose that carrier detection is routine. Among all carriers some 3% make sure that their mate is homozygous normal (AA) and some 2% decide to have no children (in addition to the normal childless rates in the population). These practices will reduce the number of fertile $AS \times AS$ matings by about 10%, leaving 90% of the original expected number. Suppose that the majority (70%) of originally expected $AS \times AS$ matings ignore the risks and reproduce normally. However, if they have an affected child, some 10% have no further children. (The average number of children born after diagnosis of the first affected child is reduced by 10%.) Among the rest (20%) of the originally expected $AS \times AS$ matings some 5% decide to have no children, some 5% opt for artificial insemination, and some 10% choose selective abortion (5% with full reproductive compensation). Since these practices reduce the number of affected individuals born, there are fewer to benefit from new treatments and fewer for natural selection to act on. The latter has the more important effect here, but both are taken into account, as described in the previous section, in deriving the combined net effect of the practices.

These figures and the changes they are likely to bring about estimated from the formulas in table 2 are shown in table 5. The combined effect of the practices would be to reduce the disease incidence by about one-third but to cause little further change in gene frequency compared to the previous change before carrier detection and before improved treatments were available. The dysgenic effects of

TABLE 5

EFFECT OF DIFFERENT PRACTICES FOR SICKLE CELL ANEMIA IN U.S. BLACKS

Practice	Extent (d)	Change in Disease Incidence (%)	Change in Gene Frequency (%)
All AS carriers:			
2. Selection of AA mate	.03	−5.9	0.2
4. Family limitation	.02	−4.0	−2.0
$AS \times AS$ couples:	(.90)		
Normal family size	.60	...	...
1. Improved fitness of cases born ($\Delta s = .3$)*	...	3.0	1.5
5. Retrospective family limitation in affected sibships ($P_r = .2$)	.10	−2.0	−0.1
5. Prospective family limitation	.05	−5.0	−0.3
6. Artificial insemination	.05	−5.0	−0.1
3. Selective abortion with full reproductive compensation	.05	−5.0	0.1
7. Selective abortion with no reproductive compensation	.05	−5.0	−0.1
Combined net effect	...	−28.9	−0.8

* Gene frequency $q = .05$; initial reproductive fitness $= 0$ ($s = 1.0$).

practices 1 and 2 are largely offset in this example by a very small reduction proposed in the reproductive fitness of all carriers.

Heterozygote Advantage

Formulas for changes in disease incidence and gene frequency have also been derived for autosomal recessive diseases where there is heterozygote advantage [5]. These confirm that many of the results will be similar to those already derived for other autosomal recessive diseases. The main differences are that (1) increases in fitness of affected individuals will give proportionally greater increases in disease incidence and gene frequency, and (2) family limitation by all heterozygous carriers will give larger percentage decreases. However, larger changes in family limitation would be needed to offset changes in fitness than if there were no heterozygote advantage.

Multifactorial Diseases

For multifactorial diseases it is only possible to calculate changes in disease incidence, since individual genes and their frequencies are not known. Formulas for calculating possible changes can be obtained by assuming an underlying continuous liability to the disease [10]. The expressions obtained are more complex than for unifactorial diseases, and the changes are dependent both on the initial incidence and on the heritability of liability to the disease [5].

In general, the greater the initial incidence and heritability, the greater the changes expected in disease incidence. The maximum increase in incidence due to improved fitness of affected individuals is likely to be about 5% per generation. This is because few affected individuals are the offspring of an affected parent.

Decreases in incidence of the same order would result if couples were detected retrospectively and reduced their family size or practised selective abortion after an affected child was detected. Larger changes in disease incidence would only become possible if individuals at high risk could be detected before they had children.

DISCUSSION

Derivation and comparison of the short-term changes expected in disease incidence and in gene frequency as a result of these (and other) practices is fairly straightforward. However, their value and relevance in practice will depend on how feasible the practices are and to what extent they are adopted in the population at large. Their feasibility, for any particular disorder, depends on having techniques for carrier detection and antenatal diagnosis as well as for early diagnosis and improved treatments. These will stem largely from laboratory and clinical research work. Unfortunately this research work will usually have to be specific to each particular disorder, and only the methodology, not the detailed results, will have a general utility. The extent to which any feasible practices are then adopted will depend on social factors such as the acceptability of the prevention methods relative to the severity and burden of the disorder, the establishment of facilities for testing, treating, and counseling families found to be at risk, and public awareness of the possibilities in prevention. The chief limitation to widespread use of prevention methods is likely to be the problem of cost in relation to benefits obtained, due to the low individual frequencies of most genetic disorders.

From the present results, there generally seems to be little cause for alarm about the deleterious effects of the new medical and social practices being adopted. It is unrealistic, as many geneticists have done, to consider the effects of one practice in isolation and to demonstrate its deleterious (or beneficial) effects, extrapolating over a large number of generations. Instead, many factors usually act concurrently but change over time, often in response to previous changes, in a dynamic system. The main deleterious effect may be from improved reproductive fitness for dominant and X-linked diseases, which can lead to substantial increases in gene frequency and in disease incidence in future generations. Yet this must be viewed in perspective. If therapy is cheap and effective, the burden of the disease to the individual and to society is slight. However, if therapy is expensive or not very effective in terms of leading a normal life, then the burden to the individual, his family, and society may be large. In this case affected families will seek ways to prevent recurrence of the disease, and society will provide medical and counseling facilities to assist in prevention and treatment.

A source of concern to the layman as well as the geneticist and physician is that the prevention and treatment of genetic disease may lead to serious irreversible deterioration of the human gene pool. Careful assessments of the dangers have already been made by Crow [11] and Fraser [2], who found them neither serious nor irreversible. Indeed, as Crow has suggested, of all the controversial

areas about the role of genetics in man, our understanding of the dynamics of the simple Mendelian forms of genetic disease is the best. The methods of prediction are reliable and the methods of selection effective. What is important is for geneticists to monitor the changes taking place and to estimate the effects of new practices. Then rational policies can be established for prevention and treatment of genetic disease, in the interests both of the individual and of society.

SUMMARY

The effects of a number of new medical and social practices on the incidence of genetic diseases and gene frequency have been studied. The results deal with short-term effects, since these are of most practical importance, and with the combined effects of several factors acting together. The size of any effects depends on the feasibility of the different practices and on the extent to which they are adopted by the population.

Most of the practices reduce the incidence of the diseases in the next generation, but some may be dysgenic. For example, improved treatment of affected individuals in dominant and X-linked diseases could lead to improved reproductive fitness, higher gene frequencies, and to an increased incidence in future generations. However, such deleterious effects may be avoided by genetic counseling or offset by other preventive practices. In recessive disorders, a small reduction in the average fitness of carriers detected by population screening would outweigh any deleterious effects of other practices. In general there seems to be little cause for alarm about the deleterious effects of the new medical and social practices being adopted.

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COMPUTERISED REGISTER SYSTEM FOR ASCERTAINMENT AND PREVENTION OF INHERITED DISEASE

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SUMMARY

A computerised genetic register has been devised for ascertaining individuals at risk and preventing further cases of inherited disease. Clinical and computer staff have co-operated to design the system. The system enables medical staff to vet data and create a series of structured files which can subsequently be interrogated in order to assess the degree of risk to individuals. Details of file structure, access modes, data chaining techniques, retrieval language and data security are presented in this paper.

INTRODUCTION

With the control of many infectious diseases and the improvement of environmental conditions, inherited disease is becoming relatively more important than in the past as a source of morbidity and mortality. For example, in a survey of child mortality in hospital it was found that some 40% of cases were due either directly or indirectly to genetic effects [1]. Because of the inherited or intrinsic nature of genetic disease, special methods are required for the ascertainment of families, assessment of risk, genetic counselling and prevention of further cases of the disease in the family. In order to integrate information from these various activities a genetic register system has been developed [2]. This paper describes the establishment of a computing system to control the data handling of this genetic register.

An approach was made by the Department of Human Genetics of the University of Edinburgh to the Regional Centre to examine the possibility of setting up a computer based register. The initial proposals for a fully comprehensive scheme were con-

sidered to be too ambitious for the resources available to both parties. By mid 1970 a simplified system had been proposed with the following specification:

1. To design and implement a file system with fast access and a good degree of security.

2. To design a data capture system which was convenient and easy to check.

3. To design and implement a suite of programs to be used for file initialisation, data retrieval and file maintenance.

Using this specification it was possible to produce a system within a year. The available resources consisted of the part time effort of staff at the Regional Centre and the Department of Human Genetics and a total of about 30 hours C.P.U. time on the Regional Centre's I.C.L. 4-75 using the Edinburgh Multi-Access System (E.M.A.S.) [3].

This economy both of financial and human resources was necessary in view of the fact that for both parties the project was one of many activities.

FILE DESIGN

From the outset it was not clear how large a filing system would be required. Clearly the size of the file would be related to the geographical area covered. In view of the Regionalisation of hospital areas it was decided to design a file system capable of holding about 25-30,000 people.

The design of the file format was dictated by the method of data capture. A pre-formatted data card has been designed to enable non-technical staff to use the system easily. The layout is arranged in such a way that a person's data falls into four categories:

1. Personal details

2. Medical details

3. Disease and family history details

4. Visit and counselling details

Once a person has been placed on the register it is unlikely that any of his personal, disease or medical details will alter, but several visits at different time may be recorded. On this basis the data file was split into two sub-files, one for the fixed data and one for the visit data. This also has the advantage of protecting at least part of the data in the event of file corruption.

With the record format defined it remained only to determine how records could be addressed directly and how to connect like records. The solution of this problem was influenced by two factors.

1. The entire system was to be run on the Regional Centre I.C.L. 4-75 under the E.M.A.S. operating system.

2. The programming language to be used was IMP [4].

The IMP language can be regarded as a subset of PL/1, but with some extra features for bit and character manipulation. Also an extremely useful direct access I/O feature was available enabling the user to transfer data easily between core and a direct access storage device.

With these available facilities a unit of information called a 'PAGE' was defined as 4096 characters. This definition coincides with the 'page size' used by the virtual addressing unit on the I.C.L. 4-75. 'PAGES' are used for both sub-files, the only difference being the number of records per 'PAGE' and hence the addressing of each record.

For the fixed data a record length of 256 characters was chosen. This enables 16 records to be held in one 'PAGE'. To address this record the user only has to know the 'PAGE' number and the record position within the 'PAGE'. It was decided to use a 16 bit address mechanism for this file, 5 bits for the record position and 11 bits for the PAGE number. This allows a maximum page address of $2^{11}-1$ or 2047 giving a total file capacity of 32,752 people. This may not appear to be an excessive number, but it should be remembered that a consultant may have several sets of files for different regions.

The addressing technique for the visit data file is the same as that used for the fixed data file. The only difference is that because the record length is shorter, 96 can be put into the 'PAGE'. This increase in the number of records requires more bits to address each one and so a 24 bit address system is used. 16 bits are used to address the PAGE and 8 bits used to

and response. The trial system is about 64 'PAGES' in total and the access times for data have been very encouraging.

The security of the data is ensured by the need for a password to log in to E.M.A.S. and a further password when a data retrieval command is given. As indicated above all data in the files is encoded and is only decoded on receipt of the correct password. For easy file maintenance several other programs have been set up. These include a program to initiate a file and define its passwords and a program to dump the direct access files onto a sequential tape file.

The computing system is now being handed over to the Department of Human Genetics for field trials leading to its full integration in the Genetic Register system. From now on the role of the Regional Centre will be that of a Consultant in implementing the system in practice.

Finally, although the system has been written in IMP and runs on an I.C.L. 4-75, the Regional Centre has developed an IMP system to run on an IBM 360 or 370. It is possible to move the entire system onto a 360 or 370 operating under O.S. and use it either in a batch mode or possibly under T.S.O. from a terminal.

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Multifactorial Models for Familial Diseases in Man

WITH DISCUSSION

BY

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Multifactorial Models for Familial Diseases in Man

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SUMMARY

Some familial diseases may be caused by many factors, genetic and environmental, acting jointly. The value and limitations of multifactorial models that have been proposed for the inheritance of these diseases are discussed. Topics considered include the complicating effects of common familial environment; the calculation of recurrence risks; discrimination between different models of inheritance; the resolution of disease heterogeneity; the use of associated continuous measurements; and the effects of selection against genes increasing liability to disease.

Keywords: FAMILIAL; HERITABILITY; MULTIFACTORIAL; LIABILITY; GENETIC DISEASE; GENETIC HETEROGENEITY; THRESHOLD; RECURRENCE RISK

1. INTRODUCTION

PROBLEMS in assessing the importance of heredity in human disease and in the expression of normal traits in man have long concerned geneticists and biometricians alike. Indeed much of the early work in biometrical statistics stemmed from problems in human genetics. So it is perhaps fitting that we should discuss some recent applications of biometrics in the study of human disease to a meeting of statisticians.

Diseases with an appreciable genetic component in their causation become proportionally more important with the decline in the frequency of diseases caused mainly by infection or by poor environment and nutrition. The number of live-born children dying in the first year of life in England and Wales has fallen from 133 per 1,000 in 1902 to 22 per 1,000 in 1960 (see Carter, 1969). However, the number certified as dying from congenital malformations has remained over this period at about $4\frac{1}{2}$ per 1,000. About 20 children per 1,000 are born with a severe or moderately severe physical malformation. Many of these conditions show familial aggregation, that is there is an increased frequency in the relatives of affected individuals, and are probably partly genetic in origin. A World Health Organisation report (1972) found that 30 per cent of admissions to one North American paediatric hospital and 40 per cent of paediatric deaths in the United Kingdom were more or less directly related to "genetic" disease.

Diseases with an appreciable genetic component in their causation can often be prevented or treated as can most other forms of disease in the population. In families with a family history of a disease, further cases may be prevented by genetic counselling, or by antenatal diagnosis and selective abortion, or by special care of individuals born at risk. Population screening programmes can be applied to couples, pregnancies or to the newborn, to allow prevention or early detection. Understanding the

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aetiology, including the form of inheritance, and the risks of genetic disease are important in work on prevention, treatment and care.

The object of this paper is to review multifactorial models of disease inheritance in man and to discuss their value, and their limitations, in theory and in practice. Section 2 gives a brief background review of diseases inherited in a simple Mendelian manner. Section 3 attempts to deal with the problem in familial diseases of distinguishing between the effects of genetic inheritance and the effects of common familial environment. Section 4 gives a formal statistical account of multifactorial models. These models are then developed and applied to various situations in the later sections of the paper.

With many authors contributing, the terminology used has become varied and often confusing, so some standardization is needed. A disease or disorder or condition, is said to show familial aggregation if the proportion affected is raised in relatives of affected individuals and genetic only if genetic effects are established. Prevalence refers to the proportion of cases existing in a population at a given time. Incidence deals with the proportion of new cases occurring in a given population over a given period, e.g. 1 year or a life time. A familial disease may be termed polygenic (if many genetic factors are proposed) or multifactorial (if many factors of unspecified type are proposed). A disease may be termed semi-continuous or quasi-continuous if it corresponds to the division of some underlying continuous scale into two all-or-none (0, 1) classes corresponding to diseased and not diseased.

2. Simply Inherited Disorders

Familial diseases in man are usually divided into three main groups: (1) those due to a single genetic locus and usually inherited in a simple Mendelian manner, (2) those due to a known chromosomal abnormality and (3) other familial diseases where groups (1) and (2) have not so far been demonstrated. Some examples of Mendelian and chromosomal disorders are given in Table 1, showing the different common forms, with the genotype of affected individuals, and the most common mating type involved. The proportion of affected offspring produced, and the risk to each subsequent child, is $\frac{1}{2}$ or $\frac{1}{4}$ for simple Mendelian disorders but very much less for incompatibilities and for chromosomal disorders. There is a large number of simple Mendelian disorders and traits known in man (McKusick, 1971) and though individually rare, these disorders are cumulatively important. Dominants outnumber recessives, probably because it is easier to establish their mode of inheritance from family material. In other species where breeding experiments can be performed, such as the mouse, autosomal recessive forms of abnormality are the most frequent.

The basis for classifying a disease as Mendelian depends mainly on showing strict adherence to the simple 1 : 1 or 1 : 3 ratios expected of genes, *x*-linked or autosomal. However, it may be difficult, even for simply inherited disorders, to establish the true mode of inheritance because many factors may distort the simple Mendelian ratios. An extensive methodology (Morton, 1969; Morton *et al.*, 1971) has been developed to estimate segregation ratios and other parameters. Many of the conditions are rare and data are hard to collect. There are problems of ascertainment of probands (index cases) and their families; of new mutations occurring; of errors in clinical diagnosis; of phenocopies (a similar clinical form of non-genetic origin); of illegitimacy; of variable family size; and of possible genetic heterogeneity (one clinical condition arising from different genetic loci).

TABLE 1

Mendelian and chromosomal forms of genetic disease

Mode of inheritance	*Abnormal genotype*	*Common parental mating type*	*Risk to the next child (segregation ratio)*	*Typical disorders*	*Number of disorders (traits) identified (McKusick, 1971)*
Mendelian disorder					
Autosomal dominant ("single dose")	a*a	a*a × aa	$\frac{1}{2}$	Achondroplasia	415[3] (528)[3]
Autosomal recessive ("double dose")	a*a*	a*a × a*a	$\frac{1}{4}$	Phenylketonuria	365 (418)
X-linked recessive	x* (♂)	x × x*x (♀)	$\frac{1}{4}$	Haemophilia	86 (64)
Maternal–fetal incompatibility	Dd	D–Xdd (♀)	< 5%	Rhesus haemolytic disease	—
Chromosomal abnormality					
Sex chromosome	XO	Normal	< 1%	Turner's syndrome	—
	XXY	Normal	< 1%	Klinefelter's syndrome	—
Autosome	Trisomy	Normal	< 3%	Down's syndrome	—

* Indicates the abnormal allele; 2—probable; 3—additional possible.

The spectrum of familial disease from simple Mendelian forms to those with complex familial patterns is well illustrated in Fig. 1 (Newcombe, 1964), which plots the frequency in sibs of affected individuals against the frequency in the general population. The dominant and recessive autosomal disorders stand out from other

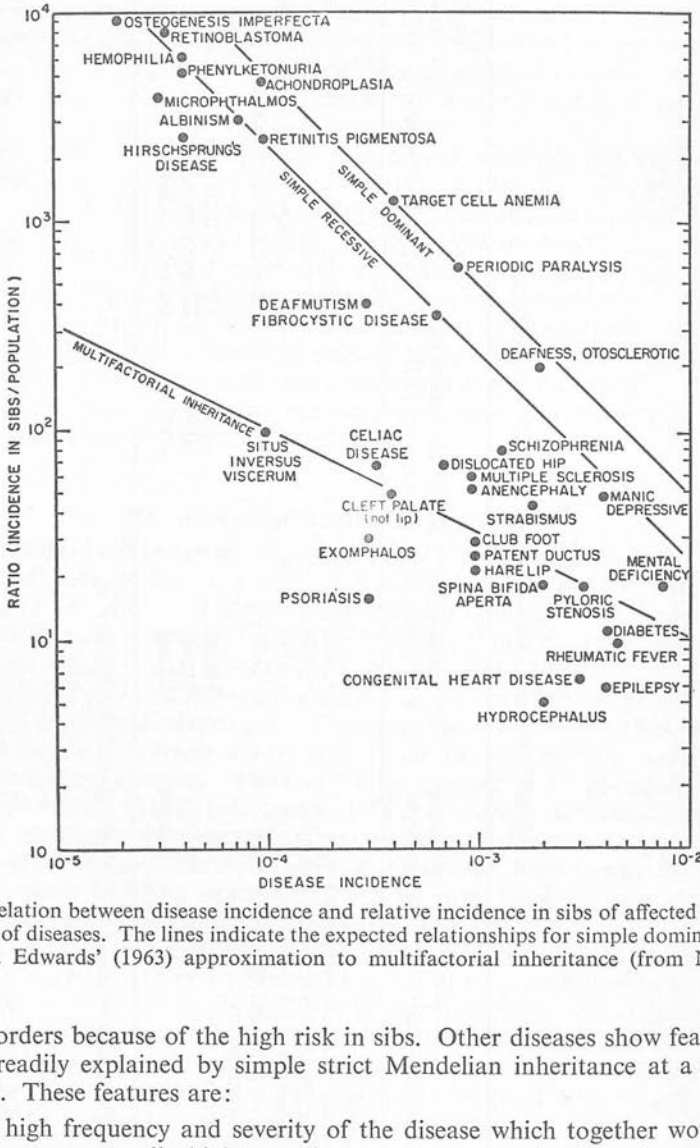

FIG. 1. Relation between disease incidence and relative incidence in sibs of affected individuals for a number of diseases. The lines indicate the expected relationships for simple dominant, simple recessive and Edwards' (1963) approximation to multifactorial inheritance (from Newcombe, 1964).

familial disorders because of the high risk in sibs. Other diseases show features that cannot be readily explained by simple strict Mendelian inheritance at a single di-allelic locus. These features are:

(i) the high frequency and severity of the disease which together would imply either an unusually high mutation rate or some selective advantage of the heterozygote form (see Section 6);

(ii) the frequency of the disease in sibs (and other relatives) of affected individuals is lower than would be expected from single locus di-allelic inheritance; and

(iii) the frequency in relatives increases as the severity and as the number of family members affected increases.

Can the effects of environmental factors added to the single locus model explain the observed familial aggregation patterns of these diseases, or do we need a multifactorial model that involves the effects of genes at more than one locus?

The single locus model can be extended to include situations where the genes at the locus do not completely determine the presence or the absence of the disease but do influence the probability that the individual will have the disease (see Section 7). These generalized single locus models, which include simple dominance and recessive inheritance as special cases, can allow for various "noise" factors in the expression of the disease, such as variable penetrance, errors in clinical diagnosis, phenocopies, genetic heterogeneity, the variable manifestation of heterozygotes and the sporadic non-heritable occurrence of the disease. An extension of the model with correlations between relatives in this variable translation of genotype into disease would allow the incomplete penetrance to be due to genes at other loci or to environmental factors common to relatives. This would be a multifactorial model but with one locus having a major effect on liability. We shall see later that there are difficulties in discriminating between single locus models and multifactorial models representing the small independent effects of many loci and many environmental factors. For this reason, and because few examples have been established, intermediate models involving two or three genetic loci will not be considered.

3. Common Familial Environment

Once we allow environment to be a causative factor in a disease, we have to recognize the fact that members of the same family tend to share the same environment as well as the same genes. Some of the correlations in disease incidence among family members may be due to common familial environments. This problem has long plagued studies of heredity in man since the environment cannot be randomized among individuals and so the effects of common family environment and common genes are confounded. Attempts to resolve this problem should be the first step in any study of familial disease in man, and yet it is very frequently ignored. Unless common familial environmental effects can be discounted or adjusted for, then estimates of any genetic parameters may be seriously in error and misleading.

The main method used to measure the importance of common familial environments is to include in the study unrelated individuals living together. This could include adopted children and their adoptive parents and adoptive sibs; spouses; relatives' spouses; and individuals in institutions. The assumption is made that choice in adoption or marriage is not directly or indirectly associated with the disease or trait being studied.

Another way to avoid the complications of common familial environments is to estimate genetic parameters from related individuals living apart. These could be adopted children and their natural parents. Alternatively, differences in relationship of related individuals living together, such as monozygotic and dizygotic twin pairs, can be used. Usually, however, the data available on such groups are limited and special searches need to be made.

A good example of the use of such materials in assessing the importance of common familial environmental effects is given for schizophrenia by Rosenthal (1970) and summarized in Table 2. Psychiatric diseases generally, and schizophrenia in particular

may be influenced by complex social relations within families. For this reason, both biological and adoptive relatives of adopted schizophrenics and of adopted controls were studied. The frequency of schizophrenia in the biological relatives of the schizophrenia patients was very much higher than in their adoptive relatives when compared with the control groups. This and other similar studies (Heston, 1966; Schulsinger, 1972) suggest that genetics is an important factor in causing the familial aggregation commonly found in schizophrenia and other psychiatric disorders. However, it must be remembered that the closeness of a biological relationship as opposed to an adoptive one is not purely a matter of genes shared.

TABLE 2

The frequency of schizophrenia in biological (first degree) and adoptive relatives of adopted schizophrenics and adopted controls (from Rosenthal, 1970)

Adopted index cases	*Biological relatives*			*Adopted relatives*		
No.	No.	Affected	Affected (%)	No.	Affected	Affected (%)
33 Schizophrenia	150	13	8·7	74	2	2·7
33 Control	156	3	1·9	83	3	3·6

4. MULTIFACTORIAL MODELS

4.1. *The Liability Model*

In one standard multifactorial model some single-dimensional quantity x, called liability, is assumed to determine the probability of an individual succumbing to the disease. The x-values may be determined both by genes and by environment. The x-value may, for example, be concerned with a development rate in congenital malformations such as spina bifida, the concentration of some biochemical product in a metabolic disease or blood pressure in hypertensive disease. All correlations in the occurrence of the disease in relatives are induced by correlations between the x-values of the relatives. If liability is determined by many genetic or environmental factors the values of x in the population may be assumed to have a continuous distribution. We can then, in theory, and without loss of generality, transform x so that it has a Normal distribution over the population with mean zero and unit variance. There is a real assumption when we assume that, in addition to the Normality of the marginal distributions, the joint distribution of the x-values for k-relatives has a k-variate standard Normal distribution. This will be assumed in all that follows.

Let $S(x)$ denote the probability that an individual with value x succumbs to the disease and $f_k(x_1, x_2, \ldots, x_k; \boldsymbol{\rho})$ denote the joint density function of the standardized k-variate Normal distribution with correlation matrix $\boldsymbol{\rho}$. In the univariate case, we shall write

$$f_1(x_1) = \phi(x_1)$$

and

$$\int_{-\infty}^{X_1} f_1(u)\,du = \int_{-\infty}^{X_1} \phi(u)\,du = \Phi(X_1).$$

The frequency of the disease in the population will be

$$P_1 = \int_{-\infty}^{+\infty} \phi(u)\, S(u)\, du$$

and the probability that all k relatives in a family have the disease is

$$P_k = \int_{-\infty}^{+\infty} \cdots \int_{-\infty}^{+\infty} f_k(u_1, u_2, \ldots, u_k;\, \rho)\, S(u_1)\, S(u_2) \ldots S(u_k)\, du_1\, du_2 \ldots du_k.$$

If we can calculate the probability of each of all possible sub-sets of relatives all having the disease, then we can calculate, by simple probability arguments, the probability of any sub-set having the disease and the rest not having the disease.

One form suggested for $S(x)$ is (Edwards, 1969)

$$S(x) = a\, e^{bx} (a, b > 0, -\infty < x + \infty).$$

This form simplifies the analysis since the density function of x among the affected members of the population is

$$\phi(x)\, S(x) \Big/ \int_{-\infty}^{+\infty} \phi(x)\, S(x)\, dx = \phi(x-b).$$

Thus the distribution of x among the affected individuals is the same as among the whole population but with the mean increased by an amount b. Unfortunately, the risk $S(x) = a\, e^{bx}$ does exceed one for sufficiently large x. Edwards' argument that $S(x)$ will only be greater than one for rare values of x is insufficient to justify results that may well be heavily influenced by rare "probabilities" appreciably exceeding one.

Great simplifications in the necessary computations result if we can assume instead that $S(x)$ is a sigmoid function. We shall assume this and write

$$S(x) = \Phi\left(\frac{x-\mu}{\sigma}\right).$$

The sigmoid function is an appropriate risk function since it increases monotonically from 0 to 1 as x increases from $-\infty$ to $+\infty$. We could allow for a base-line incidence of the disease, α, and an uncertainty of disease, $\beta < 1$, when x is $+\infty$ by defining

$$S(x) = \alpha + (\beta - \alpha)\, \Phi\left(\frac{x-\mu}{\sigma}\right).$$

In practical situations, this would require the estimation of the parameters α and β and this may well prove difficult.

We shall assume that $S(x) = \Phi\{(x-\mu)/\sigma\}$. The incidence of the disease in the population will be

$$P = \int_{-\infty}^{+\infty} \phi(x)\, \Phi\left(\frac{x-\mu}{\sigma}\right) dx.$$

We may interpret this probability as

$$P = \text{Prob}\left(z < \frac{x-\mu}{\sigma}\right),$$

where z and x are independent standardized Normal variables. Therefore,

$$P = \text{Prob}\left(\frac{\sigma z - x}{\sqrt{(\sigma^2+1)}} < -\frac{\mu}{\sqrt{(\sigma^2+1)}}\right)$$

$$= \Phi\left(-\frac{\mu}{\sqrt{(\sigma^2+1)}}\right).$$

Clearly, $\theta = -\mu/\sqrt{(\sigma^2+1)}$ determines the population incidence of the disease and σ the sensitivity of the probability of disease to changes in the value of x.

The probability that all of k relatives succumb to the disease is

$$P_k = \int_{-\infty}^{+\infty} \cdots \int_{-\infty}^{+\infty} f_k(x_1, \ldots, x_k; \rho)\, \Phi\left(\frac{x_1-\mu}{\sigma}\right) \ldots \Phi\left(\frac{x_k-\mu}{\sigma}\right) dx_1 \ldots dx_k$$

$$= \text{Prob}\left(z_1 < \frac{x_1-\mu}{\sigma}, \ldots, z_k < \frac{x_k-\mu}{\sigma}\right),$$

where $z_1, z_2, \ldots, z_k$ are independent standard Normal variables distributed independently of the jointly Normally distributed variables $x_1, x_2, \ldots, x_k$. Therefore,

$$P_k = \text{Prob}\left(\frac{\sigma z_1 - x_1}{\sqrt{(\sigma^2+1)}} < -\theta, \ldots, \frac{\sigma z_k - x_k}{\sqrt{(\sigma^2+1)}} < -\theta\right)$$

$$= \int_{-\infty}^{-\theta} \cdots \int_{-\infty}^{-\theta} f_k(t_1, t_2, \ldots, t_k; \rho^*)\, dt_1 \ldots dt_k,$$

when

$$\theta = \frac{\mu}{\sqrt{(\sigma^2+1)}} \quad \text{and} \quad \rho^* = \frac{1}{\sigma^2+1}\rho.$$

The multiple integrals in P_k can be reduced to single integrals involving univariate Normal density and cumulative distribution functions if the matrix ρ takes particular simple forms (see Curnow and Dunnett, 1962, for the general method and references).

4.2. *Equivalent and Alternative Models*

The liability and risk function approach outlined in the previous section is mathematically equivalent to the abrupt threshold model (Falconer, 1965, 1967) which has been most commonly used in practice. Earlier workers with threshold models include Pearson (1900, 1904, 1914), Wright (1934), Robertson and Lerner (1949), Dempster and Lerner (1950), Gruneberg (1952) and Crittenden (1961). In Falconer's model, a Normally distributed quantity z with variance σ^2 is added to the underlying x-value for an individual. Then all individuals with values of $y = (x+z)$ greater than a certain threshold, μ (Falconer's T), manifest the disease while those with y less than μ do not. $S(x)$ is then the probability that $z > (\mu - x)$ and is therefore $\Phi\{(x-\mu)/\sigma\}$. The larger the value of the threshold, μ, the lower the frequency of the disease in the population. There is some arbitrariness in the division between x and z when, as is assumed here, x is Normally distributed and the $S(x)$ function sigmoid. All that matters is that the z-values for different individuals must be independent. Although the mathematics is the same, the idea of an abrupt threshold is less acceptable biologically than the idea of a risk function (Edwards, 1969; Smith, 1970, 1971a).

In some of the earlier work on threshold models, approximations were involved concerning the distribution of y, $= x+z$, among relatives of individuals known to be affected. This distribution was assumed to be Normal with a different mean but the same variance as the distribution for the whole population. Edwards (1969) showed how these approximations could be avoided when disease information was available on a single relative by using singly truncated forms of the bivariate Normal distribution. Aitken (1934) derived expressions for the means, variances and covariances of jointly Normally distributed variables following truncation based on a sub-set of these variables. Mendell and Elston (1974) and Reich *et al.* (1972) used these expressions to derive frequencies in relatives and hence to obtain approximate risk estimates when disease information was available on more than one relative. These latter estimates were still only approximate because, although the means, variances and covariances were now correct, the Normality of the y distribution for relatives was assumed still to hold despite the truncation exercised on the correlated y-values of affected individuals. The method due to Smith (1970) to be described in Section 5.1 and that due to Curnow discussed earlier in this section have removed this final approximation from the calculation of risks.

To interpret the above results about the threshold model into the form commonly used in quantitative genetics, we need to assume that all of the causes of familial correlation are genetic, or that any non-genetic familial effects have been removed. Then assuming that the genetic variance is entirely additive the heritability (Falconer, 1965) of liability ($y = x+z$) can be defined, in the present notation, as

$$h^2 = \frac{\text{var}(x)}{\text{var}(x+z)} = \frac{1}{\sigma^2+1}.$$

The correlation in liability between any pair of relatives is then

$$\rho^* = \rho/(\sigma^2+1),$$

where ρ is the genetic relationship between the relatives concerned (see Section 5.1). The threshold model can be used when the genetic variance includes dominance and epistatic components providing only that the correlations of liabilities are estimated from the appropriate types of relatives or from a knowledge of the values of the various components of the genetic variance in the population studied. Care will have to be taken if there are correlations between the liabilities of parents.

In much of the work now to be described the following assumptions are made:

(i) that there are no birth-order effects,
(ii) that the x-values of parents are uncorrelated, and
(iii) that the correlations between a child and a parent and between two sibs are equal.

The last assumption would be true if the variance in x was entirely additively genetic and the environmental and infective correlations between sibs and between parents and offspring were all equal. The predictions made for other relatives require stricter assumptions such as that the correlations are entirely due to genetic effects and to the additively genetic variance.

Morton *et al.* (1970) have suggested an alternative multifactorial model for disease inheritance based on the concept of genetic load. If the risks $p_1, p_2, \ldots, p_n$ arising from each of a large number, n, of factors are small and independent, then the total risk to

an individual can be written

$$P = 1 - \prod_{i=i}^{n} (1 - p_i),$$

and approximated by the formula

$$P = 1 - \exp\left(-\sum_{i=i}^{n} p_i\right).$$

$A = \sum_{i=i}^{n} p_i$ is called the load. Sex differences and the effects of inbreeding can be allowed for but, without these complexities, the load for a relative with degree of relationship R is $A + CR$ where A is the population frequency and C is a measure of the additive effects summed over loci. Given the population frequency and the frequencies in relatives of affected individuals, values of A and C can be estimated. The model does allow dominance and, providing the exponential approximation is still sufficiently accurate, large effects on the load scale. This model will not be discussed further. In general it provides results very similar to those derived from the multifactorial model presented in this section and the single locus models with incomplete penetrance to be developed in Section 7. The only exceptions to this similarity occur when the penetrance is virtually complete or where the frequency of the disease is low and the heritability of the multifactorial model is high.

5. Applications of the Model

5.1. *Assumptions and Recurrence Risk Calculations*

Much of the application of the multifactorial model so far has been concerned with the estimation of $\rho^* = \rho/(1+\sigma^2)$, from information about the incidence (P_1) of the disease in the population and the incidence P_2/P_1, of the disease in relatives of affected individuals. We shall not discuss the detailed problems of estimation (see Reich *et al.*, 1972; Draper 1974; Mendell and Elston 1974). The relatives most usually considered have been first-degree relatives (parents, children, brothers or sisters) but monozygotic twins, second-degree relatives (uncles, aunts, nephews, nieces and grandparents) and third-degree relatives (cousins) have also been studied. If the correlations between the x-values of relatives are due to additive genetic effects at many loci, then $\rho = 1$ for monozygotic twins, $\rho = \frac{1}{2}$ for first-degree, $\rho = \frac{1}{4}$ for second-degree and $\rho = \frac{1}{8}$ for third-degree relatives. μ and σ can be estimated given estimates of P_1 and ρ^*. The single integral forms for P_k mentioned above can then be used to derive probabilities of disease patterns for some simple groups of relatives, and hence recurrence risks for individuals with particular family histories of disease. The probabilities can be used to check the adequacy of the model using information available on the frequency of familial patterns of disease and the recurrence risks can be used in genetic counselling. Curnow (1972) used the integral reductions to tabulate the risks for individuals given disease information on their parents, on one parent and one sib; or on one, two or three sibs. He also tabulated risks given information on a monozygotic twin; two such twins; or on a twin and a sib or a parent.

Smith (1971a) used numerical integration to study a wide range of family situations. Dividing the range of values of the underlying quantity into a large number of small non-overlapping intervals (i), the frequency (f_i), the probability (P_i) that an individual with underlying value at the midpoint of the interval succumbs to the disease, and the probability (P_i') that a particular relative (e.g. a sib) succumbs were

derived. The frequency of the disease among these relatives, that is the recurrence risk, is then

$$\sum_i f_i P_i P_i' \Big/ \sum_i f_i P_i,$$

where the summation is over the intervals. By increasing the number of intervals any desired accuracy can be achieved. Graphs were then drawn, for various values of ρ^*, of the frequency of the disease in relatives against the frequency (P_1) in the population. Recurrence risks in individual families given varying amounts of information, both positive and negative, about members of the family were also studied. The distributions of x for all original and all intermediate members of independent branches of the family were split into classes. The probabilities of patterns of occurrence of the disease for given sets of classes can then be added over all combinations of classes, weighted by their frequencies to obtain the recurrence risks. The method can also take account of sex and severity differences, and differences in heritability with age. For the more complex family histories approximate methods must be used (Smith 1971a). Smith also derived confidence limits for the recurrence risks. Fig. 2 shows some of the results obtained by Curnow (1972) and Smith (1970, 1971a). The recurrence risks and population frequencies are on logarithmic scales. With these scales the recurrence

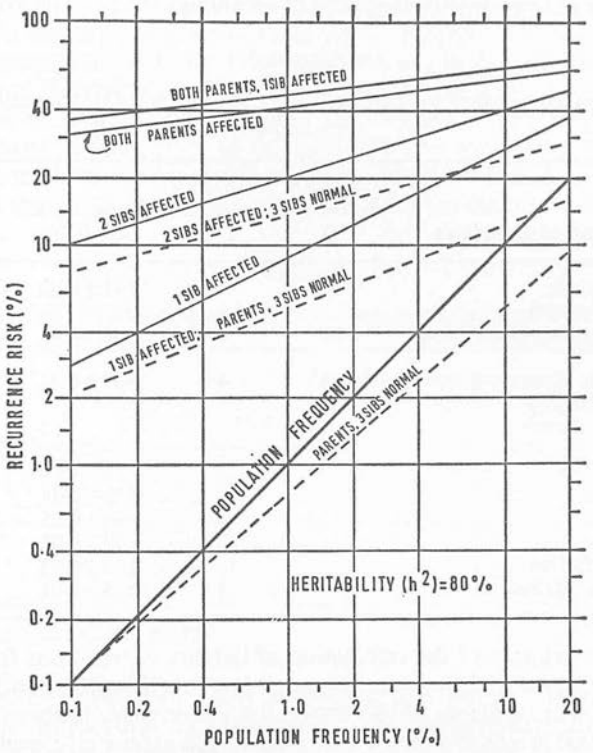

FIG. 2. Recurrence risks for multifactorial inheritance in a variety of sibships, with heritability (h^2) of 80 per cent. Broken lines include normal relatives.

risks are approximately linearly related to population frequency allowing easy interpolation. With two or more first-degree relatives affected the risks increase substantially. The inclusion of unaffected relatives decreases the risk only slightly and they may be ignored, unless the disease incidence is high.

For simple cases, for example with one relative affected, observed or "empiric" risks are available and the risks are usually low—less than 5 per cent. These risk estimates are termed empiric, because they do not depend on any genetic model. However, they are average values and do not allow for differences in risk between families dependent on their detailed family history, in terms of severity, age of onset and sex. A range of risk estimates may be needed depending on the age and sex of the individual to whom the risk estimate is to be applied. When such factors have to be considered or when there are two or more affected individuals in the family there are usually no empiric risk estimates available for use in counselling.

Further information on the family history, including information about second- and third-degree relatives, is usually available. Estimation of risks can thus become very complex and the risk may need to be evaluated uniquely for each particular family. A computer program (RISKMF) is available to do this (Smith, 1972). It takes all the above factors into account, but only approximately for second- and third-degree relatives. A series of risk tables has also been prepared for some 180 possible family histories for the major congenital abnormalities (Bonaiti-Pellié and Smith, 1974) and these may be useful in genetic counselling.

TABLE 3

Estimates of correlation in liability for some congenital abnormalities and for schizophrenia

Some congenital abnormalities	*Population frequency* (%)	*Frequency in relatives* (%)	*Correlation in liability*	*Author*
Cleft lip ± cleft palate (first-degree relatives)	0·1	3·1	0·41 ± 0·02	Carter (1969)
Spina bifida and anencephaly (sibs)	0·29	4·4	0·38 ± 0·02	Carter and Evans (1973)
Congenital pyloric stenosis (first-degree relatives)	0·30	4·0	0·37 ± 0·02	Carter and Evans (1969)
Schizophrenia	1·00			Gottesman and Shields (1967)
MZ twins		53	0·89 ± 0·06	
DZ twins		14	0·46 ± 0·05	
Sibs		10	0·39 ± 0·02	
All first-degree relatives		10	0·39 ± 0·02	
All second-degree relatives		4·6	0·28 ± 0·02	

As a simple example of the calculation of liability correlations from which complex risks could be derived, consider the condition cleft lip with or without cleft palate (Carter, 1969). The incidence of this congenital abnormality is about 1 per 1,000 and about 31 per 1,000 in sibs of affected individuals. The estimated correlation in liability among sibs from this information is $\rho^* = 0{\cdot}41 \pm 0{\cdot}02$. Correlation coefficients for several other congenital abnormalities are given in Table 3 (Bonaiti-Pellié and Smith,

1974). Correlation estimates can be derived from different groups of relatives as is shown for schizophrenia in Table 3. To compare the different estimates they have to be converted into estimates of heritability of liability, $1/(1+\sigma^2)$, by taking account of the degree of relationship, ρ, between the relatives and by removing or discounting any common familial environmental effects contributing to the correlation. Significant differences among heritability estimates from different relatives, or heritabilities exceeding unity may suggest that dominance or epistasis may be important, that the multifactorial model may not apply or that non-genetic familial effects have not been adequately discounted.

5.2. *Sex and Age Effects and Differences in Severity*

In estimating the correlation between the liability, x, of relatives, there are often complications because the disease may occur with varying severity and the disease frequency may depend on age and sex. In some disorders the sex with the lower incidence often has the higher frequency of affected relatives. This apparent reversal of frequencies is quite consistent with the multifactorial model. This is because the sex with the lower frequency will have its risk function $S(x)$, $= \Phi\{(x-\mu)/\sigma\}$, displaced to the right of the risk function for the other sex. Hence, an affected individual of the sex with the lower frequency will probably have a higher x, or liability value, than affected individuals of the other sex. Their relatives will also tend to have higher liabilities and so a higher proportion of them will be affected. A good example of this is given by the congenital abnormality pyloric stenosis, in Table 4. Females are less frequently affected but their relatives are at higher risk and the pattern appears confusing. However, when the correlations are estimated from the different sets of relatives (comparing the frequency in relatives with the population incidence in the same sex) the anomaly in the frequencies is largely resolved and the estimates can be pooled to give a single estimate of liability correlation for the disorder.

TABLE 4

Analysis by sex of familial frequencies in pyloric stenosis (after Falconer, 1965)

		First-degree relatives			
		Male		*Female*	
Proband	*Population frequency* (%)	*Frequency* (%)	*Correlation in liability*	*Frequency* (%)	*Correlation in liability*
Male	0·5	5·0	$0{\cdot}32 \pm 0{\cdot}04$	2·2	$0{\cdot}37 \pm 0{\cdot}06$
Female	0·1	17·1	$0{\cdot}48 \pm 0{\cdot}05$	6·6	$0{\cdot}47 \pm 0{\cdot}07$

Pooled estimate $0{\cdot}40 \pm 0{\cdot}025$.

To take account of different levels of severity of a disorder two, or more, risk functions differing in location, i.e. in μ, can be used corresponding to the different severity classes. Similarly, the onset age of a disorder, such as diabetes, may be associated with liability and a range of risk functions may be constructed for the different age groups.

Moving the risk function, $\Phi\{(x-\mu)/\sigma\}$, relative to the mean of the liability distribution changes only μ, not σ. A further possibility would be to allow differences in σ, and hence in heritability for the two sexes, for different age groups and for different severity classifications.

Several other factors may be more difficult to take into account in analysis, such as (1) differential mortality of affected individuals (Smith *et al.*, 1972; Draper, 1974), (2) inappropriate or unreliable estimates of incidence (Smith, 1974) and (3) different rates of detection and diagnosis for patients and for relatives (Smith, 1974).

5.3. *Concordance in Twins*

Monozygous (MZ) twins have the same genotype, so if a condition is entirely genetic in origin, concordance in MZ twin pairs should be complete, as it is for the strict Mendelian disorders. This is rarely the case in the common familial diseases. Often the MZ concordance rates are quite low, even for conditions which would otherwise be thought to have an important genetic component. Here the concordance rate is the proband concordance rate, i.e. the proportion of affected co-twins of independently ascertained affected individuals. In fact low concordance rates are expected with the multifactorial (MF) model, especially in conditions with low population prevalence, as shown in Fig. 3 (Smith, 1970). This is because the prior risk to any individual with a given "genotypic" liability, is low and so, assuming no environmental correlation, the risk to an MZ co-twin with the same genotype as his affected twin is also low.

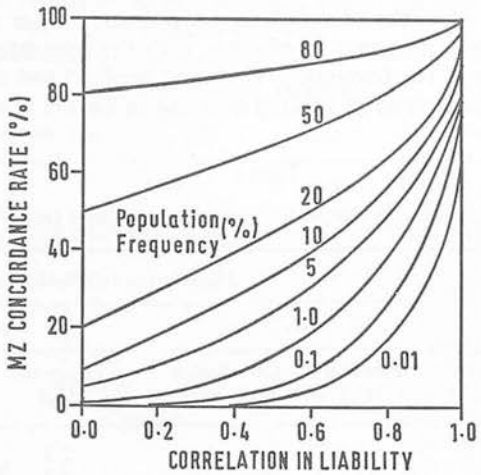

FIG. 3. Expected "proband" concordance rate in monozygotic (MZ) twins given the population frequency and the correlation in liability (from Smith, 1970).

This result may remove some of the confusion in comparing results in twins and other relatives. For example, estimates, from relatives other than monozygotic twins, of the heritability of clubfoot (talipes equinovarus) range from about 0·60 (Wynne-Davies, 1970) to 0·68 (Ching *et al.*, 1969). However, these estimates seemed to conflict with Idelberger's (1939) result of a 33 per cent concordance rate for monozygotic twins. Yet, with a population incidence in Caucasians of 0·12 per cent,

Fig. 3 shows that a concordance rate of 33 per cent is in fact not too low but instead is rather high, for heritabilities in the range 0·60–0·68.

5.4. *Resolution of Genetic Heterogeneity*

The frequency of one disease in relatives of patients with another disease can be used to measure the degree of genetic association between two diseases or to resolve genetic heterogeneity. This procedure is, of course, used intuitively by physicians in grouping or resolving various clinical forms or groups of disease. A simple 2×2 χ^2 test of the numbers with form 1 and with form 2 among relatives of patients with form 1 and of patients with form 2 can be used to test for complete association. For example, spina bifida and anencephaly are usually classified as different abnormalities but they run together in families as shown from data of Carter *et al.* (1969) in Table 5. The 2×2 χ^2 of the numbers in Table 5 was not significant and, with similar results from other studies, the two forms are usually considered as different manifestations of the same genetic disorder.

The same procedure can be elaborated and quantified using the multifactorial model of disease liability. Given two groups—separated on any criterion, clinical, biochemical or statistical—the genetic correlation in liability (Falconer, 1967) can be estimated as

$$h^2_{12}/\sqrt{(h^2_{11}\, h^2_{22})} \quad \text{or} \quad h^2_{21}/\sqrt{(h^2_{11}\, h^2_{22})},$$

where h^2 is heritability, the first subscript refers to patients and the second to relatives, and 1 and 2 refer to the two disease groups separated. For example, in Table 5 the estimates of genetic correlation between spina bifida and anencephaly are very high, showing that the two conditions are closely associated and can be treated in risk estimation and in genetic analysis as one condition. Similarly to test for genetic independence, a null hypothesis of a genetic correlation of zero can be tested. Note that if a disease is made up of two or more independent sub-groups, then the heritability of the combined condition will be decreased (not increased as suggested by Edwards, 1969).

Falconer's (1967) simple method for estimating the genetic correlation in liability between two diseases or groups depends on assuming that the genetic correlation is zero, or is unity (Smith *et al.*, 1972). If it is intermediate then the method is not strictly appropriate due to overlapping of the distributions of the two forms. However, it has been found (Smith, unpublished) that the simple estimates of the genetic correlation will give a very good indication of the true genetic association between the two groups and is unlikely to mislead the investigator in interpreting his data.

5.5. *Associated Continuous Traits*

So far, estimates of recurrence risks have used only the disease status, normal or affected, of relatives. Often there is additional information on graded or continuous traits associated with the condition that can be incorporated to improve the estimated risk in a particular family. For example, blood pressure in hypertension, intra-ocular pressure in glaucoma or blood glucose levels in diabetes could be measured in the person at risk and in relatives and these would be informative in estimating recurrence risks for these diseases. The trait may define the disease, be a factor in its causation or be a result of the disease. Alternatively, the trait might be a measure of environmental factors involved.

TABLE 5

Genetic association of anencephaly and spina bifida (data from Carter et al., 1969)

		Sibs								
			Anencephaly			*Spina bifida*			*Combined*		
Patients	*Population frequency* (%)	*Total No.*	*No.*	*Frequency* (%)	h^2_{ij}	*No.*	*Frequency* (%)	h^2_{ij}	*No.*	*Frequency* (%)	h^2
Anencephaly	0·36	707	16	2·26	$0{\cdot}46 \pm 0{\cdot}07$	13	1·84	$0{\cdot}36 \pm 0{\cdot}06$			
Spina bifida	0·42	854	20	2·34	$0{\cdot}48 \pm 0{\cdot}06$	32	3·75	$0{\cdot}58 \pm 0{\cdot}04$			
Combined	0·78	1561							81	5·19	$0{\cdot}58 \pm 0{\cdot}03$

Genetic correlation estimates		
Patient	*Relative*	*Genetic correlation* $\{h^2_{ij}/\sqrt{(h^2_{ii}.h^2_{jj})}\}$
Anencephaly	Spina bifida	$0{\cdot}71 \pm 0{\cdot}20$
Spina bifida	Anencephaly	$0{\cdot}92 \pm 0{\cdot}19$

The important assumption that will be made here is that the risk of the disease is related to the continuous trait only through the latter's correlation with the liability, x. The effect of knowing the value of the correlated trait in the individual or in some relatives is then simply to change the mean values of the liabilities and the variances and covariances of these liabilities. As before, Aitken's (1934) formulae for the adjustment of variances and covariances to allow for truncation on these variables can be used to obtain approximate risk values (Smith and Mendell, 1974). The approximation again being that truncation on other variables has affected means, variances and covariances but not the Normality of the distributions. Curnow's exact method based on reduction of risks to single integral forms can be used when information is available on the individual and one relative and to more extensive situations providing the pattern of the liability correlation matrix takes the required structural form (Curnow, 1974). The approximate results (Smith and Mendell, 1974) agree well with the exact results derived by Curnow (1974) when only one relative is involved but the accuracy when several relatives are involved is not yet known.

The mean, variance and heritability of the correlated trait can be estimated from data in the usual way. The correlation between the trait and liability is estimated from a comparison of the mean values of the trait for affected and for unaffected individuals.

The calculations made show that estimates of risk can be substantially changed by inclusion of data on the associated trait. The overall value of the associated trait in increasing the precision of the risk estimate will depend on its correlation with liability to the disease. A good measure of its value is the additional proportion of the variation in liability accounted for by the associated trait, above that explained by the information on disease status (Smith and Mendell, 1974). If the correlation with liability is low then the trait adds little information and if the correlation is high then the individual's own value for the trait (as one's own blood sugar level in diabetes) gives a better estimate of liability to the disease than all the family history. Thus it is largely when the correlation between the trait and liability is intermediate, or when the individual at risk cannot be measured, perhaps because he is too young or not yet born, that an associated trait will be used with family history in risk estimation. A computer program (RISKCT) is available to do the necessary calculations.

Hopefully, clinical research will lead us to a fuller understanding of the nature of the liability, x. The results obtained about the relevance of a correlated trait include as special cases the trait being x itself or being an estimate of x subject to error. We are therefore able to test hypotheses that particular measurable quantities are x or estimates of x. It must be remembered that we have not assumed that x determines the occurrence of the disease, but only that x is a partial determinant of the disease that includes all the factors leading to correlations between the incidence of the disease in relatives.

If the underlying variable is identified, then a series of thresholds can be selected and estimates of the correlation in liability between relatives can be derived for each threshold level. Reich *et al.* (1972) found good agreement in estimates of the correlation for data on the number of lung tumours in mice exposed to urethane. However, Trimble (1971) working with some half a millon records on birth weight in man found highly significant differences between estimates from thresholds at different parts of the distribution. He was unable to get a transformation to a Normal distribution and concluded that the methods may be very sensitive to departures from Normality and warned against uncritical application of the models.

6. Disease Frequencies and Selection

Natural selection is continually reducing the frequency with which individuals with certain diseases reproduce. This will lower the frequency of any genes that increase the liability to these diseases. It is therefore reasonable to ask why so many diseases with a genetic component in their causation have not been eliminated from the population.

Severe recessive diseases tend towards an equilibrium in which the incidence of the disease is equal to the rate of mutation from the normal to the harmful form of the gene at the locus concerned. Mutation rates are thought to be of the order of 10^{-5} or much less (Cavalli-Sforza and Bodmer, 1971) so the balance between natural selection and mutation may explain the frequency of many of the recessive inborn errors of metabolism such as phenylketonuria, with its frequency of about 7×10^{-5}. The selection pressure against one of many genes acting additively, or otherwise, on liability in a multifactorial model will be less than the pressure at a single locus fully determining the occurrence of the disease. This will result in higher equilibrium frequencies for the harmful genes.

Another possible mechanism for maintaining deleterious genes in populations is a selective advantage for heterozygotes over both homozygotes. The best known example of this is sickle cell anaemia which is caused by a recessive allele. Heterozygotes for the sickling allele have a fitness some 25 per cent superior to that of normal homozygotes in areas where malaria is endemic. The recessive homozygotes have very low fitness and the frequency of the diseases in malaria areas is about 10 per cent. Similar, but unknown, mechanisms have been proposed to account for the high frequency of some of the inborn errors of metabolism such as cystic fibrosis in Caucasians. A 2 per cent advantage in fitness for heterozygotes over the normal homozygotes is almost sufficient to account for the current frequency of the disorder (5×10^{-4}) but an advantage of only 2 per cent would be very difficult to detect in practice, particularly since heterozygotes cannot, as yet, be reliably distinguished from normal homozygotes. Individual loci in the multifactorial model may also have genes held in equilibrium by similar forces.

Genes could also be held in equilibrium if individuals with a high liability value but not suffering from the disease had a slight superiority in fitness compared with individuals with a low liability value. A reduced fitness for individuals with low liability values would result in the preferential selection of individuals with intermediate liability values. This could lead to equilibrium gene frequencies but doubts exist about the stability of such equilibria (Robertson, 1956; Curnow, 1964).

So far in discussing selection we have assumed that large populations are involved. An abnormally high frequency of some Mendelian and multifactorial disorders in small isolates and in some populations may be due to the founder effect or to the random drift of gene frequencies (Rao and Morton, 1973).

Even with large populations, the relevance of equilibrium results depends on a constant environmental and genetical background for selection and mutation over many generations. The changes in gene frequency each generation are often small, of the order of the mutation rate or the selective pressures at individual loci. We may therefore be observing the effects of genes that previously had selective advantages or disadvantages but are now moving slowly towards new equilibria or towards elimination. For example, consider a gene that was previously at equilibrium as a recessive for a lethal disease but the disease has been harmless for the last t generations.

The gene frequency will be

$$q_t = 1-(1-u)^t(1-u^{\frac{1}{2}}).$$

With $u = 10^{-5}$, it takes 130 generations to multiply the gene frequency by $\sqrt{2}$ and hence double the frequency of the now harmless disease.

7. Discrimination between Different Modes of Inheritance

Is it possible to discriminate between the different modes of inheritance proposed for familial diseases using data likely to be available? Edwards (1960) in a now classic paper showed that it would be very difficult to discriminate between different modes of inheritance. All models tended to give similar familial patterns of frequencies so that differences in, for example, the predicted fall-off of incidence with decreasing genetic relationships, would be slight.

Moreover, a great variety of genetic models could be proposed for testing. Work in this area has tended to try to discriminate between a single-locus, two-allele model and the multifactorial model. If the methods used cannot discriminate between these extreme models, it is unlikely that they will be able to discriminate between intermediate models. Even with continuous traits there are difficulties in deciding whether a major gene is involved or in estimating the number of loci that are influencing the character (Elston and Stewart, 1973; MacLean *et al.*, 1974). These difficulties are bound to be greater with 0, 1 characters such as diseases that can be treated as having a single level of severity. Of course, it will never be possible, without identifying the loci concerned, to prove that a certain genetic model applies. It may be possible to disprove certain models if they provide an unsatisfactory fit to the observed data. Unfortunately, in practice the observed data may be biased from various factors, such as familial environmental effects, genetical and clinical heterogeneity, errors in diagnosis and in parentage and biases in ascertainment of families and in estimation of population incidence. The discovery and use of associated variables closely correlated with liability (see Section 5.5) might make discrimination between different models easier.

The strict Mendelian one-locus two-allele model can be generalized as follows:

Genotypes	A_1A_1	A_1A_2	A_2A_2
Frequency	q^2	$2q(1-q)$	$(1-q)^2$
Proportion manifesting the disease	f_{11}	f_{12}	f_{22}

A recessive gene with complete penetrance would have $f_{11} = f_{12} = 0$, $f_{22} = 1$ and a dominant gene with complete penetrance $f_{11} = 0$, $f_{12} = f_{22} = 1$. The expected proportions of each genotype among affected individuals and the expected frequency of the genotypes (and so of the disease) in relatives of affected individuals can be derived (Campbell and Elston, 1971; James, 1971). Note that this model assumes that there are no other genetic factors, common to relatives, to modify the expression of the major locus. This is biologically unlikely. It has been shown with laboratory animals that penetrance can often be modified by selection. However, it provides an extreme model with which to contrast the multifactorial model.

Elston and Campbell (1970), Wilson (1971) and Kidd and Cavalli-Sforza (1973) have fitted the above model, using maximum likelihood methods, to familial frequency data on schizophrenia and obtained a reasonable fit with several parameter sets (for example, $q = 0{\cdot}06, f_{11} = 0, f_{12} = 0{\cdot}08, f_{22} = 1{\cdot}0$, i.e. all homozygotes and 8 per cent of heterozygotes for a particular allele manifest the disease). Chung *et al.* (1974) have also applied the model to sibship segregation data on cleft lip (with or without cleft

palate) with results of a similar form. The multifactorial model with only two parameters also gave a reasonable fit to the data, so no resolution between the models was possible. However, the best fitting multifactorial models did imply higher recurrence risks in sibships than the single-locus model.

Krüger (1973) and Smith (1971b) have tried to determine in what situations discrimination between these extreme models of inheritance would be possible. Their approach was to generate data by computer on one model and to test the fit achieved to it by the other model, and vice versa. It was found that even with large numbers of individuals and neglecting sampling fluctuations, for a wide range of situations one model could generally satisfactorily fit (as judged by χ^2 goodness of fit tests) the data generated by the other model. This was true both for the data on the incidence in particular relatives aggregated over families, as well as for data on segregation within sibships. The single-locus model could always fit data from the multifactorial model, except when, as for many of the "common" congenital abnormalities in man, the correlation between relatives was high and the incidence of the disease was low. On the other hand, if a fairly strict Mendelian situation applied, the multifactorial model would usually be readily rejected. In summary, a set of parameters for the single-locus model could usually be found which fitted the multifactorial data, but not vice versa. Some of the parameter sets obtained for the single-locus model were rather extreme, and not very acceptable biologically. It may therefore be appropriate to include a term for the prior probability of obtaining an extreme parameter set and weight the likelihood of the two models appropriately.

Some theoretical insight into the problem of model discrimination was given by James (1971), who showed that there were only three independent estimable parameters in the generalized single-locus model, namely the disease incidence and the additive and dominance components of the genetic variance in incidence. Thus an infinite set of $q, f_{11}, f_{12}, f_{22}$ values will fit any set of data that can be fitted at all. The single-locus model cannot give rise to any epistatic genetic variance (i.e. variance due to interaction between loci) while the multifactorial model can. However, with the multifactorial model epistatic variance in incidence is only large when the heritability is high and the disease incidence is very low (Dempster and Lerner, 1950) and so discrimination may only be possible in these situations, confirming the results from the computer simulations described above.

A method to discriminate between the models, depending on identifying different levels of manifestations of the disease, or equivalently multiple thresholds, has been proposed by Reich *et al.* (1972). With two or more thresholds the expected familial frequencies, especially for MZ twins, may be different for the two models and so discrimination may be possible. They applied their model to data on the number of induced lung tumours in mice. Selecting two threshold levels (11 and 18 tumours, respectively) they were able to reject ($P < 0{\cdot}005$) a single-locus model but not the multifactorial model of liability. In practice, it may be difficult to identify two thresholds, or to get them far enough apart, for adequate discrimination or to ensure that the thresholds occur on the same scale of liability (see Section 5.4). Moreover, rejection of the single-locus, two-allele model does not exclude other simple models such as one locus with multiple alleles, or two loci.

So as to use concurrently all the information in each family, Elston and Stewart (1971) have developed a generalized method of analysing family histories. They have given methods for writing the likelihood of a pedigree and then of finding the maximum likelihood estimators of parameters given data from a number of families. Different

modes of inheritance can be proposed and the fit to different models compared. By using all the information in the pedigree concurrently these methods should be more powerful in discriminating between different modes of inheritance than any of the methods described previously.

Another approach has been developed by Morton and MacLean (1974). Their concern is to test if, in addition to many loci with small effects, a locus with major effects exists. So they have specified a model with both multifactorial and single-locus components. Rather than rely only on the binomial variate, normal or affected, they have included a continuous trait, such as glucose tolerance levels in diabetes, in defining the liability of an individual. Analysis of a continuous variate may be five to ten times more powerful in detecting a major locus, than for a binomial trait, and initial trials with simulated data suggest that any loci with major effects, defined as more than 1 standard deviation difference between the two homozygotes, could be detected (MacLean *et al.*, 1974).

These and other methods are being used to try and resolve the inheritance of many familial diseases. However, the biological interpretation of the statistical results may not be satisfactory or reliable. Only when individual loci associated with the disease can be identified will the question be resolved. This will depend more on laboratory and clinical research, rather than statistical analysis. A good example of this is given by the condition ankylosing spondylitis. This disease has a frequency of 4 per 1,000 with recurrence risks in first-degree relatives of about 4 per 100. Previous genetic analyses had concluded that the condition was inherited either as an autosomal dominant with penetrance of 70–80 per cent or as a multifactorial disorder with a heritability of liability of $70 \pm 9{\cdot}3$ per cent (Emery and Lawrence, 1967). However, recently Brewerton *et al.* (1973) found a very close association of the disease with the allele W27 at the histocompatibility locus HL-A, with 90–95 per cent of affected individuals having this allele compared with about 5 per cent in the normal population. Thus the disease is largely inherited as an autosomal dominant with a penetrance of 8 per cent in males and 1 per cent in females. This major locus affect was not detected by the methods described earlier. Actually, frequencies in second- and third-degree relatives give heritability estimates over 100 per cent, but the standard errors are large and biases in these relatives are difficult to discount. This example highlights the danger in concluding that inheritance is multifactorial simply because reasonable heritability estimates are obtained.

In the current state of knowledge about many diseases, the choice that may have to be made is between a single-locus model with incomplete penetrance and a multifactorial model. The multifactorial model with its two parameters, μ and σ, or P_1 and $\rho^*(h^2)$, often appears to be adequate to describe the available facts—the population frequency, the risk to first-degree relatives and other relations, and the concordance rates in monozygotic twins. A single-locus model with incomplete penetrance could also nearly always be found to explain the data because such a model, even with additivity at the locus, has three parameters—the risks for the two homozygotes and the gene frequency. The advantage of the multifactorial model is that it requires fewer parameters.

8. Different Genetic Models and their Effects on Estimating Recurrence Risks

The recurrence risks for the single locus model can be derived from first principles from the Mendelian frequencies and segregation ratios (e.g. Elandt-Johnson, 1971,

Chapter 7). To carry out the calculations, Heuch and Li (1972) have developed a computer program, PEDIG, that gives the risks with the single-locus model for any family history. Computer programs to calculate recurrence risks with the multifactorial model have already been referred to in Section 5.1.

For simple family histories all the models will tend to give good, and therefore similar, risk estimates. This is because their parameters are directly derived from the empiric risks. The difficulties mentioned earlier in discriminating between different models do imply a certain robustness in derived risk estimates to the particular model used. Two questions arise, (1) do the different models lead to different risk estimates in more complex family histories? and (2) how well do the estimated risks compare with any empiric risks available for complex families?

Comparisons with empiric risks for complex family histories are few because of the difficulty in collecting sufficient families with several affected individuals. Multifactorial risk estimates for diabetes were in reasonable agreement with empiric risks calculated from familial data (Darlow, 1972). On the other hand, empiric risks with two or more affected relatives for cleft lip $\pm$ cleft palate (Woolf, 1971) were substantially higher than the multifactorial or single-locus risks estimates (Chung *et al.*, 1974).

Morton (1969) has suggested a further model to obtain recurrence risks for sibs when the disease risks are variable between families. Using a method due to Skellam (1948), he assumed that the distribution of risk p, between families was a Beta distribution with parameters α and β:

$$f(p) = \frac{p^{\alpha-1}(1-p)^{\beta-1}}{\beta(\alpha,\beta)}, \quad 0<p<1.$$

The population incidence is $\alpha/(\alpha+\beta)$, and the frequency in sibs of an affected individual, is $(\alpha+1)/(\alpha+\beta+1)$. α and β can be calculated given values of the population incidence and the incidence in sibs of affected individuals. In general, the recurrence risk, given s sibs with r affected is $(\alpha+r)/(\alpha+\beta+s)$. The values of α and β for sibships with 0, 1 and 2 affected parents can similarly be derived. Smith (1971a) and Mendell and Elston (1974) compared the predictions of this model with the multifactorial model and found good agreement when only one or two sibs were affected but less good agreement if there were more affected individuals in the family when the multifactorial model usually gave the higher recurrence risk estimates. Van Regermorter and Smith (1974) studied risks derived by the single-locus and Beta models for a range of parameter values which were compatible with selected heritability values for disease liability. When the penetrance of homozygotes was high, the recurrence risks were fairly similar for all three models. However, as the penetrance fell the risks for the single-locus model reached a plateau equal to the penetrance level and did not increase with further affected relatives. Thus different single-locus parameter sets, fitted to the same observed data, may lead to quite different estimates of recurrence risk.

9. DISCUSSION

The main value of the multifactorial model has been as a statistical tool to summarize data on frequencies of familial disease into standard and interpretable statistics. The results for diseases can be couched in the same form, correlations or heritabilities, as for continuous traits and so are easily understood. Tests can be made between results from different relatives of those affected and from different populations. If estimates are similar they can be combined to give a single estimate of the relative

importance of heredity in the aetiology of the disease. If they differ, they may give guidance as to the mode of inheritance or to the other factors, environmental or genetic, affecting liability to the disease. An important property of the estimate of the heritability of liability is that it is not a direct function of the level of the incidence of the disease. Many of the earlier summarizing statistics, such as Penrose's K ratio, (P_2/P_1^2) in our notation, Penrose (1953), Edwards' empirical result $P_2 = P_1^{\frac{3}{2}}$, Edwards (1963) and Holzinger's (1929) "index of heritability", were not successful in separating the concepts of "heritability" and the level of disease incidence.

The multifactorial model generally gives very similar results to the single locus model with incomplete penetrance. The multifactorial approach is no more difficult computationally and is, we believe, often more plausible.

The main antagonism to the model has arisen because many workers have concluded, on finding that the model fits, that in fact inheritance must be multifactorial. This non-logical step is hard to avoid, but can lead to serious errors in interpretation. For example, several quantitative traits known to be largely controlled by a single locus with multiple alleles may mimic multifactorial inheritance (Eze *et al.*, 1974) and finding a locus closely associated with ankylosing spondylitis (see Section 7) should warn of the dangers of false inferences.

Two important uses of the model, in estimating recurrence risks and in discriminating between modes of inheritance, have been covered in the previous sections. These applications depend more on computing than on advanced mathematics. Providing a model with which to contrast simple Mendelian models of inheritance may prove important, since if tests fail to detect major loci segregating for the disease, some form of inheritance which will tend to the multifactorial model may be assumed by default, and its results and implications will apply at least as an approximation.

There is often confusion about the interpretation of heritability and the possible effects of environmental change. With a fixed relation of risk to liability, heritability here is concerned with the genetic variation in liability about the current mean and tells little about shifts in the mean value due to "environmental" changes. Falconer (1965) has suggested that the only guidance it can give is that when the heritability is high it shows that current variable environmental factors, including nutrition and forms of preventive treatment, have little effect on liability so that it may be wise to look for new and novel factors to change the mean liability and hence the frequency or severity of the disease. A criticism of the interpretation of heritability is made by Kidd and Cavalli-Sforza (1973). They showed that the choice of the underlying genetic model has an important effect on the conclusion about the "proportion of the variation in liability due to genetic factors". By fitting a single-locus, two-allele model to data on schizophrenia they found that only 10–15 per cent of the variation in liability was due to differences in mean liability between genotypes. This compared with estimates of 80 per cent or higher for the heritability of liability using the multifactorial model on the same data. suggesting a much greater importance of genetic effects. However, Kidd and Cavalli-Sforza's model is biologically unlikely since it allows only environmental factors and no genetic factors to modify the expression of the major locus. Moreover, since the genetic values of their genotypes differed substantially, their result is not due to the absence of important genetic effects, but rather to the low frequency of the deleterious allele and of the abnormal homozygote compared with the other genotypes. The operational usefulness of components of variance or of heritability, which is a ratio of variance components, calculated on the scale of incidence is far from clear. The practical relevance of heritability depends on its use

as a regression or correlation coefficient in predicting the consequences of selection applied to a population. This in turn depends on the characteristic concerned being a continuous Normally distributed variable.

The multifactorial model has been used so far largely to summarize data and its possible use in splitting a disease into various clinical sub-groups with different aetiologies (see Section 5.4) has not been fully exploited.

In many respects the multifactorial model is a simplistic and "lumping" approach and Nature is likely to be much more complex and heterogeneous. With intensifying biochemical, serological and clinical research, separate entities in familial disease are continually being identified and isolated. For example, in coronary heart disease identification of various lipo-protein fractions allow new approaches to study the inherited and environmental factors associated with the disease. Thus the role of the multifactorial model in familial disease may be as a temporary tool useful during a period of ignorance for estimating risks and for providing indicators about the relations between different diseases and the relation of diseases with measurable continuous characters. Major breakthroughs must come from more fundamental research. What are the familialy correlated elements of liability and what are the familialy independent components that determine the incidence or non-incidence of disease at a given level of liability? These will be the important questions in the future.

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DISCUSSION OF THE PAPER BY PROFESSOR CURNOW AND DR SMITH

Dr C. O. CARTER (M.R.C. Clinical Genetics Unit): I am very happy to propose a vote of thanks to Professor Curnow and Dr Smith. My background to this is almost entirely non-mathematical, but I have been collecting family data for years on common congenital malformations and other reasonably common conditions which clearly have some degree of genetic determination. These curious features, which the authors have described, were early apparent: first, the fact that consistent family patterns were obtained which were

different from those from straightforward Mendelian inheritance; secondly, that the relatives of the less commonly affected sex were more often affected than those of the more commonly affected sex; thirdly, the cumulative effect, in that if two individuals in a family were affected already there was a higher recurrence risk than when one member only was affected; fourthly, the effect of the severity of the malformation on the recurrence risk—and so on.

Early on, in the 1960s, thinking about these points in relation to pyloric stenosis and cleft lip, I proposed a multifactorial aetiology with the genetic component being polygenic. But I do not have the mathematical ability to work this out properly. In 1960 John Edwards had already made a major contribution, which I had not read at the time or I would have received some help from it.

I was delighted when the agricultural geneticists, who were much more familiar with this kind of subject than we were in relatively simple medical genetics, moved into the field. Professor Falconer's first paper was a revelation to me, explaining and quantifying many of the observations I had made. It gives me great pleasure to see this being developed further.

I think some difficulties remain—again, I was pleased to see the discussion of twin concordance in tonight's paper. I felt instinctively that a high twin concordance was not needed on any threshold model because the pairs could be nicely balanced on either side of the threshold, but it was interesting to see it quantified. However, it is still something of a problem, particularly with congenital malformation, because not only do monozygotic twins have the same genotype, but they *prima facie* grow up in precisely the same intra-uterine environment—yet there is still only 20–30 per cent concordance for many of these common malformations. It might be expected to be higher because of the common environment.

For genetic counselling, clearly we look with interest at the predictions based on developments of the multifactorial model. Again, I think we must be a little cautious here because, as Professor Curnow and Dr Smith said, these conditions may be heterogeneous and nearly always there is a relatively rare component of single gene conditions mixed up with the multifactorial which cannot always be distinguished. We are able increasingly to distinguish them; for example, there is a type of cleft lip and cleft palate which behaves as the simple dominant condition, which can be picked out because there are mucous pits in the lower lip. When we see the kind of family in which the father has had cleft lip, also two of his children and, later, one of these children has had an affected child, even though there is no mucous pit present we have to ask ourselves whether we are dealing with yet another single gene condition, one which cannot be distinguished. We would tend to give a higher risk to a relative than that calculated from the polygenic, multifactorial model.

It seems to me that tonight's authors may not have brought out sufficiently the value of the second- and third-degree relatives in distinguishing between the multifactorial and the modified single gene inheritance. It is in the second- and third-degree relatives that the heritabilities of over 100 per cent begin to appear if the polygenic model is applied to a modified single gene condition. For some conditions—not all—we have good data on second- and third-degree relatives; for example, cleft lip.

Overall, however, looking at these mathematical developments from the sidelines I have found the last 12 or 13 years extremely stimulating and enjoyable. I should like to thank our two contributors tonight for giving such an excellent review of the developments over this period of time and have great pleasure in proposing the vote of thanks.

Professor J. H. EDWARDS (The United Birmingham Hospitals): It is with some hesitation that I accepted this challenge. I am a consumer, rather than a producer, and, since I am involved in advising patients with familial disorders, I would welcome any numerical aid which would lighten my burdens and clarify theirs. I feel in the position of having to

decide whether we are dealing with something which, to take two broad categories in a similar situation, may be chess or warfare. Are we dealing with a highly formalized situation, which has to be accepted and discussed for its elegance and intellectual stimulation, or with something crude and practical? Not being able to follow some of the deeper incursions into the infinitesimal calculus, I find myself in the position of an experienced general and amateur chess player who is asked to comment on a game between experts.

I should like to take the empirical view, which seems to be a tradition of this Society, and ask the question whether this approach bears fruit or flowers. To my mind, the authors have given us an elegant procedure which bears flowers, but I do not feel that it bears fruit. As chess is regarded as a more intellectual activity than warfare, and flowers more elegant than fruit, this need be no criticism.

There are three points on the "fruit" which I shall discuss.

First, I do not regard it as a matter of fact that there is an increasing proportion of familial disease. This has always struck me as a surprising statement because the diseases of the past, which were mainly of infectivity and of unhealthy and hostile environments, are intensely familial. The Brontës coughed all over each other: Edward Gibbon's six succeeding brothers—all, for good measure, called Edward Gibbon— died in infancy. The diseases are becoming mellower now, and they are probably becoming less familial.

I think that the concept of familial disease is a confusing one because it is difficult to imagine a non-familial disease. We are all exposed to the conditions to which the flesh is heir, and there are, by definition, no disorders in man—or likely to be—to which the flesh is not heir. I cannot conceive of a disease irrelevant to the genetic background.

Secondly, the question of models. There is the implication that some statisticians consider that biologists are wandering about trying to fit models to things. In fact, in the days of the ultracentrifuge, the electron microscope, and the genetic code, the time for this is past, just as it is past in such subjects as geography, mechanics and the planetary system. We have a basic model, and the residual problems are of estimation and not of decision. We are not really in the position of a blind man wandering about looking for shoes, who goes into a hat shop and finds they do not fit, and then into a glove shop with the same result, and eventually goes into a shoe shop and feels that he has arrived. We are in the position of somebody who goes straight to a shoe shop, and then has problems of exact fit. There is no problem of genetic models: we have a complete Lego set provided for us by the molecular biologists, which leads to the expected consequences. We have one set of Lego only—there are no alternative models; all these so-called models grade into each other and provide only estimation problems.

One way in which we can try to plot this is rather simple (Fig. 1). If we have a large number of loci, we can take the effect of any allele at any locus, as a_i, and frequency at that locus as p_i. This can be summed over each locus, and also over all loci. The loci

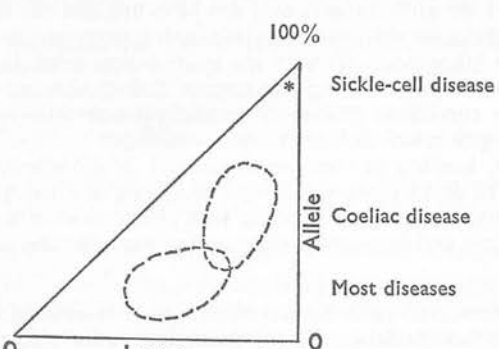

FIG. 1.

are very large in number, running to hundreds of thousands—there is room for millions. The alleles are more limited in number, so that, at most loci, any pair chosen at random are likely to be identical.

Given that this is our only endowment, we have to ask ourselves what is the strongest allele (which a_i is the greatest—where a_i is the ith allele), which is the most influential allele at one locus (which $a_i p_i$ is greatest) and which is the most influential locus, at which is the sum of $a_i^2 p_i$ greatest. These are all slightly different, but are questions which need to be asked.

The specification of "amount" is difficult. One solution which is simple, although it has not been very productive, is to use contributions to variance. Once this specification is made we can plot the proportion due to the strongest or the most influential allele and also to the most important locus, both going from zero to 100 per cent.

If we take a disease which is inevitably the consequence of some specific allele, for instance, sickle-cell disease or Tay–Sachs disease, then it is represented by a point at the apex of the triangle as shown.

There are some diseases in which there are many alleles at one locus which considerably influence the incidence; for instance, coeliac disease and myasthenia gravis, which are greatly influenced by alleles at, or near, the HL-A loci. There are many alleles and the strongest must be somewhere near the point shown. All the diseases to which the flesh is heir must lie within this triangle; all of them must have a strongest allele, and a strongest locus. It seems that we have an estimation problem at this level, not a decisional one. The problem is to find where they are.

This makes a difficult and very interesting estimation problem—and estimation appears to be what is needed in advanced sciences, in which there are few remaining yes–no questions. Genetic linkage is a scientific activity in which significance tests can be justified, but there are now few fields of biology in which a significance test can be done without admitting a degree of ignorance which is inappropriate.

The third point at issue is how to give an opinion to somebody who is asking for advice about a recurrence risk. There are various genetic correlations, or relationships: there is the sib/sib, and the parent/child genetic correlation which is of 0·5, and the cousin/cousin relationship of 0·125. In an ideal situation of complete genetic determination, the phenotypic correlation will be equal to the genetic correlation. People are worried about the risks of disease, first, because they have seen the diseases from which their relatives have suffered, they know it is unpleasant and think of it as *the* disease about which they have to worry. Secondly, because they know that diseases tend to run in families. At least, most people seem to know this.

There are some extremely good data for this purpose, much of it collected by Dr Cedric Carter. Given a defined relationship to a victim of some disease, the risk of affliction necessarily is monotonic with the degree of resemblance defined by this relationship. We have this sequence of risk, which is never 100 per cent, although it may be 50 per cent or so in an identical twin. If we take the logarithm of this incidence, this is linear against the phenotypic correlation on the exponential or logistic model (Edwards, 1968) (Fig. 2). So we can plot a line through a series of points connecting the extremes of unrelated individuals (the population incidence) and the incidence in identical twins. It does not have much meaning, and it is difficult to conceive a relationship which would give a genetic correlation in the intervening levels, but a regression line can be plotted. The practical point is, given the data points and the line, on which is the advice to be based. I think that the advice should always be given on the data, not on the regression line, so I do not find this concept of regression of practical utility. Fortunately, the level is so low that it does not usually cause problems. But this is a situation in which one has to work on the raw data, and there is no way in which those raw data can be "cooked" and made more useful by taking, not a datum, but the intercept of the regression at that point.

A further point in relation to using the term "heritability" in this context is that it is an emotive word because it sounds rather like heredity and it is easy to obtain the impression

that they are simply connected. Of course, they are connected if one is experienced at adding together the variances but, in the mundane world in which distinguished observers such as Jensen require an armed guard—partly because they themselves fail to appreciate the formal irrelevance of heritability values to opportunities for environmental benefit—it must be accepted as easily misunderstood.

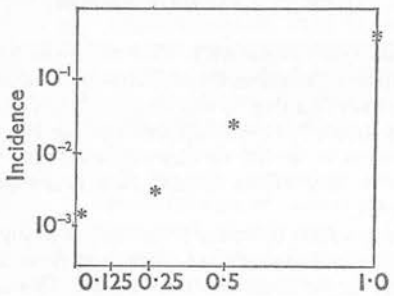

FIG. 2.

The animal geneticists use the parameters environment squared (e^2) and genetic contribution squared (g^2), and define the heritability (h^2) which is the proportion the genetic contribution bears to the sum of both. This is useful in predicting the degree of response to breeding. In man it is rather more confusing, although the alphabet is very helpful. There is a parameter, which might be called "domesticity", d^2, which is the non-genetic familial environment. There is g^2, the genetic component. These two added together give the familiarity or f^2. There is also the non-familial environment e^2: that is, the environment in the classical sense. We therefore have a large number of parameters and, in practice, usually just two degrees of freedom. (The bulk of the information in a pedigree can be summarized by the three possible types of unordered sib-pair.) What can be estimated in man is not heritability, but familiarity. This has a number of advantages as a concept because, even if 100 per cent, it does not imply any limitations on environmental response.

Having said that I did not feel that the fruit was actually fruitful, I might go on to an aspect which I find more exciting and interesting, perhaps because I am less able to understand it: that is, to the flowers. We have to try to provide some simple way of handling these very complicated functions, and the Gaussian curve itself is quite complicated. Indeed no two statistical books seem to give exactly the same method of handling it, in part, because it is written in a peculiar form. It can be written

$$1/\sqrt{(2\pi e^{x^2})}.$$

This makes it a little easier to understand but, even so, it is complicated and the usual method of integration is confusing, requiring acts of faith even in advanced textbooks. Obviously, if there are two variates it is even more complicated and, in the general case, has no algebraic solution. It is surprising that this problem has become such an unfashionable pursuit because, in 1897, Sheppard made the interesting observation—which he proved—that in the symmetrical case

$$r = \cos\{a/(a+b)\}\pi.$$

This is rather remarkable as it might be thought that it would never equal one; this is no problem because in the familial case it is never zero as it becomes increasingly elliptical.

This leads to the approximation $z = (\pi/8) \log_e (ad/bc)$† which is empirically very robust, rather surprisingly, and it does not seem to matter much where the thresholds are (Edwards, 1957, 1969). This is an important point because the effect of the environment is to move the thresholds around. Thus, in the case of this identity, it would seem to me that heritability is formally irrelevant to the possibilities of environmentally improving a disease—tuberculosis is now so rare that its infection is difficult to acquire, although Karl Pearson thought that immigration should be suppressed because this highly *heritable* disease would become rampant due to the *genetic* contribution of the various groups of immigrants who were coming into the country at that time. There are excellent reasons for stopping the immigration of people with tuberculosis, but "heritability" is hardly relevant.

In 1904 Karl Perason, with his remarkable aptitude for integrals, solved the bivariate problem with the tetrachoric coefficients, and explored and tabulated this model which Professor Curnow kindly attributed to me—but this was in 1904, 65 years earlier. He and Everitt tabulated this (Everitt, 1910), and their infinitesimal integrations were confirmed by Dr Smith's electronic enumerations. It might seem like fishing with a worm to check on Karl Pearson's algebra with a computer, but those of us who want fish are very glad that this has been done.

Finally, there is the difficult problem, the three-dimensional system in which there are parents and a child, the four-dimensional system when there are two children. This defeated Karl Pearson and empirical studies are impractical on a computer because, if sufficient slices are taken, there is insufficient time and space. It now seems to have been solved completely, in special cases, although I am afraid that I cannot follow Professor Curnow fully on his algebra. This remarkable achievement seems to give results which are consistent with observations. The only disturbing feature is that some of the lines in their figure cross.

I should like to thank the authors very much for their "flowers"; to be distinguished for both flowers and fruits is too much for most plants, and is hardly to be expected in the field of mathematics. I hope that in the published edition of this paper Professor Curnow will give a little more space to his integral, since it is elegant and brief, and is part of the solution to this extremely difficult problem of the generalization of the multivariate normal hypersurface.

It is a pleasure to second a vote of thanks for a paper which so concisely describes what would be expected on plausible assumptions, and which has, in part, been confirmed by the empirical studies of integration over finite intervals.

The vote of thanks was passed by acclamation.

Mr G. J. A. STERN (London N.6.): I would hesitate to comment on this paper, had the authors not brought in some non-statistical considerations which affect us all. I mean that they appear to advocate selective abortion for cases where there is an appreciable risk of the child being born with a partly hereditary disease or malformation. We are talking about ending a life on the grounds of a possible disability, and we need to see with what degree of certainty such disability can be predicted.

The recent controversy popularly associated with the names of Jensen and Eysenck on inheritance of I.Q. level shows that there is by no means universal agreement either on the degree of heritability of some qualities or on the models and methods used to establish that degree. To the outsider, it looked as if convincing arguments could be made on both sides, at least as far as the racial aspects were concerned: would this be the case here if similar political passions were aroused?

The authors give correlation in liability for some abnormalities and defects, but these correlations are usually low; often only 0·3–0·5. Some of the higher levels quoted relate

† Where the symbols a, b, c, d, refer to the volumes of a doubly dichotomized bivariate distribution.

to twins, which, while very relevant to the theory, have no direct applicability to genetic counselling, for one cannot selectively abort one twin because the other has a defect. The authors admit that they cannot verify which of several models they use is the most appropriate, and inside the models they detail quite far-reaching assumptions as to distributions etc. They place weight on several studies made on the heritability of schizophrenia. Yet schizophrenia is difficult to diagnose with certainty, and one can imagine that in many cases knowledge of the fact that the parent was schizophrenic may have affected the diagnosis. In short, it seems that in most cases all that can be said is that there is an appreciable probability of the child being born with a disability, but that the odds in favour of a healthy child are still far better than even. Is there not something repulsive and all too reminiscent of Nazi ideology and practice in abortion on such grounds? What will surviving children feel about parents who would have had them aborted on suspicion in this way?

It seems to me that such studies are valuable (not that my praise or blame is of consequence), but that there is danger of forgetting the human dimension. The seriousness of the condition is hard to predict, as is the degree to which the person, or advances in medical science, can overcome it. Let us recall the case of Christy Brown, the celebrated Irish novelist. I daresay that not one case in 100 of those cited by the authors was as hopeless as Christy Brown's—paralyzed except for one foot, and unable to talk comprehensibly, so that he was long thought to be mentally retarded. Yet he is now a best-selling novelist (operating an electric typewriter with his foot) and has got married. He is fortunate in having escaped the genetic counsellors, and society is fortunate that he did so.

It is also true that quite apart from medical advances, the human being can often overcome many serious conditions so that hardly any trace remains. Yet all these possibilities for improvement, at least as significant and beneficial as the Moon expeditions, will be literally aborted if current policies continue. Let us find out about heritability of disease, certainly, but let us not use this knowledge for the easy way out of final solutions which impoverish the human race and strangle advances in healing and care.

The following contributions were received in writing, after the meeting:

Dr O. MAYO (Waite Agricultural Research Institute, University of Adelaide): In Section 6, discussion of cystic fibrosis as a possible selectively balanced polymorphism does not take account of (a) the fact that the 2 per cent advantage required to maintain the disease at its current frequency is far less than the presumptive advantage conferred by the observed differences between genotypes in fertility (which were claimed to be the source of the heterozygous advantage), (b) the possible effects of population size on the frequencies of such traits (Robertson, 1962) and (c) the probability that there is genetical heterogeneity in this disease (e.g. Polley and Bearn, 1974). It is still fair to say that the polymorphisms associated with malaria remain the only ones where convincing evidence of balanced polymorphism exists.

The discussion of the associations between polymorphism and disease, while directed towards discrimination between different modes of inheritance (Section 7), does not do full justice to the vast body of data on such associations. That between HL-A and ankylosing spondylitis is only the most recent and dramatic, allowing, as it apparently does, the reclassification of this disease as unifactorial; it may well be that similar conclusions could be drawn for many others if the genetical resolution were as fine as is possible for the HL-A system. In addition, the use of information from associated or linked loci for the resolution of genetical heterogeneity and prediction of liability should not be discounted; as is implied in Section 5.4, this can readily be incorporated into the general framework used by the authors, yet they mention specifically only the newer technique of using information from associated continuous traits (Section 5.5). While the magnitudes of the risks to persons of different genotypes are rarely as disparate as in the HL-A–ankylosing spondylitis case, the differences are not everywhere negligible.

Professor T. REICH (Washington University): The excellent description of multifactorial models presented in this paper suggests a number of comments concerning the analysis of family data for psychiatric disorders. In general, the multifactorial models are suitable for the analysis of these data, since at the outset they do not require the assumption that environmental effects common to relatives are absent. Furthermore, the number of parameters required to define the models is small when compared with other theoretical modes of disease transmission, allowing many hypotheses to be tested which may otherwise be approached only with difficulty.

Diagnostic validity

The first problem which must be faced in studying psychiatric disorders is the problem of diagnostic classification. For all of the major functional psychiatric disorders, several systems of classification are in use. Often heterogeneous entities are grouped as a consequence of outmoded theories about their aetiology. Usually, severe or definite cases are universally recognized, but there is poor agreement about mild or border-line cases. For example, schizophrenia is defined in Europe as a severe disorder with many persistent psychotic symptoms, and the population prevalence is approximately 0·85 per cent (Slater and Cowie, 1971). The most popular American criteria for schizophrenia include these severe cases, but also include mild cases whose illness may not be protracted. The prevalence of this wider form of "schizophrenia" is approximately 4 per cent (Kety *et al.*, 1973). Using computational techniques analogous to those described in Section 5.4 of this paper, it can be determined whether the two types of schizophrenia are drawn from the same liability distribution, or whether they represent two independent entities. The observation that these two entities can be represented along the same phenotypic dimension would validate an expanded concept of the disorder and provide additional classes of information for analysis.

Mild or subclinical analogues of major psychiatric illness, such as alcoholism, manic-depressive illness and anxiety neurosis have also been defined, and by repeated application of the anlytic techniques described in this article, an increasing proportion of the population can be defined with respect to the liability to develop these disorders. In this way, new thresholds in the liability distribution can be specified and recurrence risks can be improved, both with respect to the probability of being affected and the kind of disorder which may occur.

Since genetic components are not required, determination of the relationship between varieties of a disorder may proceed using family data where common environmental effects are present. Assumptions about the relationship between the correlations for different classes of relatives are not required (i.e. a separate correlation may be estimated for parents, siblings and half-siblings) and sources of error due to nongenetic familial effects, assortative mating and selection are minimized.

Environmental heterogeneity

The multifactorial models described here may not only be used to resolve questions of genetic heterogeneity, but also to investigate the effects of environmental heterogeneity. Using an approach suggested by Falconer (1952), the concept of a trait is broadened to include the environment in which it occurs. If a population of affected individuals is divided into two or more groups, the estimation of correlations, and cross-correlations between relatives for these "traits" may greatly improve our understanding of environmental effects on the incidence of a disorder and on its transmissibility from parent to offspring. It is possible that our understanding of what constitutes a "relevant environment" may be altered and programmes for the prevention of these disorders may be improved. It must be remembered that multifactorial models take the population prevalence into account, so that the effect of environment on the transmissibility of a disorder can be directly assessed.

Alcoholism is approximately four times as common in men as in women. Reich *et al.* (1975) used a multifactorial model to investigate the phenotypic differences between alcoholism in male and female populations and were able to conclude that nonfamilial environmental factors could entirely explain the sex-effect. By contrast, Cloninger *et al.* (1975) investigated antisocial personality in males and females and were able to show that the large sex-effect could be represented by two thresholds in the same liability distribution. These latter findings supported the view that nonfamilial environmental sources of variation were equal in the two sexes.

The additivity assumption

Assumptions of additivity made when estimating genetic components have been a persistent source of acrimonious debate in behaviour genetics. In the present context, correlations and cross-correlations between relatives can be estimated from different points on the liability distribution and the additivity assumption used in defining the liability can be tested. The detection of interactions depends on the number of available thresholds and on the distance between them. Even though the assumption of additivity is robust, major interactions may be detectable with a large sample. Heterogeneity based on severity, sex-effect and polymorphic symptomology provides natural phenotypic distinctions between affected individuals and may offer opportunities for detecting non-additive interactions. In addition, independently transmitted subvarieties of a disorder may be detected and removed from the data set, resulting in a more homogeneous residual. This approach may be contrasted with the use of carefully normalized scales for measuring behavioural traits where non-additive interactions may be concealed when the trait is normalized.

It is my opinion that the first step in understanding the genetics of a psychiatric disorder is a methodologically sound analysis of the correlations between relatives when common environmental effects are present. These analyses can be helpful in defining the entity to be studied, in recognizing independent varieties of the disorder, and in broadening the concept of a trait, so that a larger population of affected individuals can be studied. The multifactorial models of disease inheritance can be most useful in these investigations.

Professor I. I. Gottesman (University of Minnesota): As a fairly satisfied user-consumer of the multifactorial models so neatly and comprehensively reviewed by Professor Curnow and Dr Smith, I would hope that their efforts would reach a deservedly large audience, larger than the Royal Statistical Society. I say this because the applicability of their methods goes beyond the 4½ per 1,000 congenital malformations and the 20 per 1,000 infants born with significant physical malformations to many forms of mental retardation (4 and 20 per 1,000 respectively for severe and mild retardation (Roberts, 1973) and to many conditions with later ages of onset such as ulcer, diabetes, hypertension and concomitants of ageing itself (e.g. senility and variation in the age at death from so-called natural causes). I suggest supplementing their excellent list of references with a few items to emphasize these points as well as the agricultural origins in plant and animal breeding of the multifactorial models: Lerner (1958), Jinks and Fulker (1970), Mather and Jinks (1971) and Fraser Roberts (1973).

I find the given definitions of polygenic and multifactorial diseases (Section 1) perpetuating an unintended ambiguity that has haunted us since the arguments between the Mendelians and the biometricians at the beginning of the century; the definitions are not mutually exclusive. Nowadays everyone recognizes that genes have pleiotropic effects, that the phenotype of interest can be modified by environmental factors, and that the phenotype of interest can be modified by the genetic background of the gene or genes of interest. The definitional problem stems in part from the gap between population genetics and clinicians, on the one hand, and physiological genetics, on the other.

Grüneberg (1952) pointed out that "the multiple genes of quantitative genetics are in fact nothing but genes whose remote effects only are being studied" (p. 110). It is necessary to avoid confusion by noting that some phenotypic traits in man are associated with major monolocus effects, genetic background effects, and poly-environmental effects while others are associated with poly-locus (polygenic), genetic background, and poly-environmental effects; the term "multifactorial" does not help us distinguish between these two classes as acknowledged at the end of Section 2. The distinction that can be made by the locutions above is blurred at the level of gene action as well as by the recognition that some genes in a polygenic system may have much larger effects than others (cf. Wright, 1934; Thoday, 1967; Gottesman and Shields, 1972). If I have added to the confusion, I apologize.

I have reserved my main comments for uses made by Curnow and Smith of data from the study of schizophrenia in the biological and adoptive families of schizophrenic probands. I would have expected them to use data on diabetes mellitus given the greater experience with this disease and the more reliable diagnoses that provided the data (e.g. Falconer, 1967; Simpson, 1969; Smith *et al.*, 1972). Shortly after Falconer's seminal 1965 paper on the inheritance of liability to threshold diseases was published, James Shields of the Institute of Psychiatry, Maudsley Hospital, and I recognized the probable usefulness of the approach to the analysis of data we had been collecting on schizophrenic MZ and DZ twins, their co-twins and their other relatives. We were able to visit Falconer in the summer of 1966 and have worth-while discussions that led to our introducing his liability model to the behavioural sciences (Gottesman and Shields, 1967, 1968). Unresolved questions we raised were later solved by Falconer (1967) and Smith (1970). Further advances by Smith (1971a) permitted us to compare the predictions of a polygenic theory of schizophrenia with those of Slater's specific dominant gene with incomplete penetrance theory and with the appropriate pooled empirical observations from the systematically conducted studies in the literature (Gottesman and Shields, 1972). The population prevalence and the heritability of liability value we used to generate the polygenic predictions were dictated by another analysis we performed in an effort to find a convergence point from various data sets that were more extensive than those appearing in Curnow and Smith's Table 3 under our names. Fig. 3 shows the results we obtained for the heritability of the liability to schizophrenia by the triage of six different population prevalences for monozygotic and dizygotic twins, the sibs, the offspring of two schizophrenics and the second-degree relatives. As a consequence we chose a value of 1 per cent for the population prevalence and a heritability of liability of 80 per cent, the nearest tabled value in Smith (1971a), to generate predictions for the risks to probands' sibs and children as a function of the number of parents affected with schizophrenia. The results are shown in Table 1 and confirm Curnow and Smith's conclusions about the difficulty of distinguishing between single locus and multifactorial modes of inheritance for common disorders.

The points in Section 3 about the confounding effects of common familial environment are well taken but are not as well made as they might be. An expanded discussion of the problems is given by Cavalli-Sforza and Feldman (1973) and Rao and Morton (1974). The data presented in Table 2 (Section 3) do make the point that schizophrenia occurs in the biological relatives of adoptees who became schizophrenic and at much higher rates than in the adopted relatives who reared them. However, the majority of the biological relatives were half-sibs and not first-degree relatives as labeled; further, the proportion of relatives shown as affected with schizophrenia actually consists of definite plus uncertain diagnoses of schizophrenia plus a hard-to-define category of "schizophrenia spectrum disorder". The problems of dealing with the latter are formidable (cf. Shields *et al.*, 1975) even with the aid of the suggestions from Reich *et al.* (1972); cf. Cloninger *et al.*, 1975). In an update of the data on adopted Danish schizophrenics (Kety *et al.*, 1975) 173 biological relatives have been identified for the 33 probands; of the former 66 are parents, 41 are maternal half-sibs, 63 are paternal half-sibs and 3 are full sibs. The prevalences (without age-correcting) of definite and then definite plus uncertain schizophrenia in the paternal half-sibs are reported and permit further efforts at fitting to the two models in our Table 1

above. We get an embarrassment of "riches". The prevalences in half-sibs of 13 and 22 per cent correspond to 1·6 and 3·0 per cent in control half-sibs. Using Smith's (1970) graph the correlation in liability for half-sibs becomes 0·45 and then 0·56; both figures lead to heritabilities near 200 per cent. If the data are used to calculate the penetrance of a posited dominant gene (Slater and Cowie, 1971) with frequency 0·03, the values are too high to be credible. At this point of model "unfitting" we cannot tell whether the data or the models are "embarrassed".

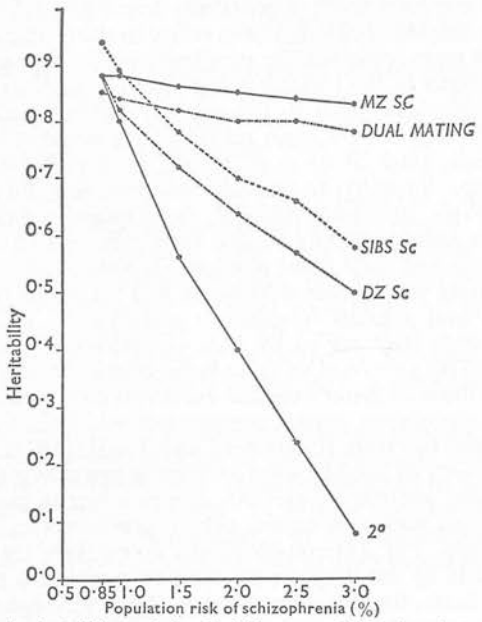

FIG. 3. Smith-type heritabilities of the liability to schizophrenia as a function of varying population risks, estimated from risks in different classes of probands' relatives (from Gottesman and Shields, 1972).

TABLE 1

Schizophrenia risk as function of parent status
(Source: Gottesman and Shields, 1972)

	Risk (%)			
	(a) *To probands' sibs*		(b) *To probands' children*	
No. of parents affected	0	1	1	2
Observed, pooled risks	9·7	17·2	13·9	46·3
Predicted, polygenic	6·5	18·5	8·3	40·9
Predicted, monogenic	9·4	13·5	8·8	37·1

Curnow and Smith provide their own best caveats about the limitations of multifactorial model fitting when they conclude, "Thus the role of the multifactorial model in familial disease may be as a temporary tool useful during a period of ignorance for

estimating risks and for providing indicators about the relations between different diseases and the relation of diseases with measurable continuous characters. Major breakthroughs must come from more fundamental research." And earlier (Section 7), "Of course, it will never be possible, without identifying the loci concerned, to prove that a certain genetic model applies." Although it leads to unsung heroism, the methods reviewed by Curnow and Smith permit the disproof of models or at the least their thoughtful revision after further data collection. The compatibility between data and a particular model is a necessary but not sufficient condition for the credibility of the model. The heuristic value of sophisticated multifactorial models for generating collaborative research among clinicians, biostatisticians and molecular/developmental biologists must be acknowledged and praised.

The authors replied in writing as follows:

We are grateful to contributors to the discussion for their interesting comments.

We agree with Dr Carter that second- and third-degree relatives could be very useful in discriminating between different models of inheritance and have shown this empirically elsewhere (Van Regermorter and Smith, 1974). However, because of the lower degrees of relationship, large numbers of such relatives will be required, for example to get heritability estimates with low standard errors, and the information on these relatives is often less reliable than on first-degree relatives.

The value of genetic linkage and associations with genetic markers, stressed by Dr Mayo, for discriminating between simple and complex forms of inheritance is doubtful, for these have not been very productive in the past, for a summary see Mayo (1972). However, with the advent of several strong HL-A disease associations, the value of these methods may have to be reconsidered, as we indicated.

Our intentions, as applied statisticians in medical genetics, are to measure, understand and predict the occurrence and recurrence of these familial diseases. We wish to provide clinicians and families with information about possible forms of inheritance and about risks, so that individuals can make informed decisions about their families. There is neither compulsion nor advocacy, such as Mr Stern suggests, in genetic counselling, but rather, as in other fields of medicine, clinicians working to improve the health and welfare of their patients. This is not to deny the difficult moral issues associated with abortion.

Our terminology "familial disease" for a disease which "runs" in families does not please Professor Edwards but we like its generality. Common genes cannot be implicated until common familial environmental effects have been discounted. Professor Edwards states that heritability (g^2) cannot be estimated in man, but only familiarity (f^2). The whole point of including Section 3 in the paper was to consider and refute this argument and to show that (g^2) can be estimated free from (d^2), the domesticity component. Thus, if Karl Pearson had studied unrelated persons (e.g. spouses) living together, or relatives living apart, he would have found that non-genetic common familial effects were very important in tuberculosis and would have moderated his counsel accordingly. In another part of his remarks Professor Edwards suggests that because we know the basic model of inheritance (DNA and the genetic code) there can be no further models to test in genetics, and so only estimation problems remain. This would be a sorry state of affairs for any science, and would sadden Karl Popper. However, with the organizational complexity of the genome and of the phenotype deriving from it, there are many interesting models to test despite having only one form of building brick. Edwards' Fig. 1 and his remarks about HL-A illustrate this point well. Coeliac disease with a major effect of the HL-A locus now falls in the middle of his diagram. What about diabetes, schizophrenia, the congenital abnormalities and all the other familial diseases? Does a locus with a major effect exist for these conditions? This is a hypothesis we may be able to test, after defining a "major effect". The outcome of the test may then determine how to allocate genetic research effort for these diseases. Similarly we have indicated that tests for genetic identity

in related diseases, such as early and late onset diabetes, or for genetic heterogeneity within a clinical condition, may be useful.

In saying that research with the multifactorial models has borne little fruit, Professor Edwards has ignored much of the material presented and discussed in the paper. The model gives an explanation, and an understanding, of many of the empirical findings which were otherwise difficult to reconcile, and Dr Carter spoke about this in his remarks. Indeed Professor Gottesman advocates greater scope and use of the model for the wide array of familial diseases in man. Our work with estimation of recurrence risks deals, not with the simple cases indicated in Fig. 2 in Professor Edwards' remarks for which we have empiric risks, but with risks in families with a more complex family history for which there are no empiric risk estimates, and with continuous traits which may be associated with a disease. These should be useful in assessing risks of disease in relatives, so that preventive measures may be applied, and in genetic counselling about the risks to future children.

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inal muscular atrophy – resolution of heterogeneity

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e spinal muscular atrophies (SMA) may be defined as a group of familial disorders aracterised by degeneration of the anterior horn cells of the spinal cord and/or bulbar tor nuclei but with no pyramidal tract or peripheral nerve involvement. Different forms SMA can be recognised according to whether the distribution of predominant muscle kness is proximal, distal, bulbar, scapuloperoneal or facioscapulohumeral. With the ception of those forms of SMA in which weakness is mainly proximal, these broad groups be further subdivided on the basis of clinical and genetic criteria. In fact, it has been gested that some 18 or so different forms of SMA (Table I) can be identified on the s of clinical manifestations and mode of inheritance (Emery, 1971, 1973). There is e debate, however, as to whether or not on the basis of these criteria heterogeneity be resolved within the proximal group of SMAs, particularly where onset is before lthood.

The aim of this paper is to present some of the methods available which might be used esolve the problem of heterogeneity within this latter group of disorders. These methods illustrated with data from clinical and genetic studies reported in the more recent litera-, as well as from material collected in this Department. Altogether data on 338 families 4 affected individuals) with proximal SMA in at least one member of the family and ere onset was before adulthood, have been analysed. In all these families the diagnosis SMA had been firmly established on the basis of muscle histology and/or electromyo-phy. Sources of these data are given in the Appendix. It has to be remembered that re is a weakness in all such studies because of the inevitable heterogeneity between s of data reflecting the differing interest of clinicians in various forms and aspects of A. For this reason the analysis of these data can only be considered exploratory.

METHODS FOR RESOLVING HETEROGENEITY

thods which may be used to resolve heterogeneity in neuromuscular disorders are mmarised in Table II. For example, the demonstration of a primary biochemical defect some patients but not in others would clearly delineate a specific form of SMA. Un-tunately a primary biochemical defect has not yet been demonstrated in any of the SMAs. Tests for allelism consist of studying the offspring of parents who are both affected by a essive trait and are clinically similar. If the parents are homozygous for genes at different then all their offspring will be normal, but if they are homozygous for the same gene all their children will be affected. This approach has been used, for example, to demon-

TABLE I *Suggested classification of the spinal muscular atrophies* *

- *A. Proximal*
  - I. Infantile
    - Autosomal recessive
      1. Without arthrogryposis multiplex congenita
      2. With arthrogryposis multiplex congenita
  - II. Intermediate
    - ? Autosomal recessive
  - III. Juvenile
    1. Autosomal recessive
       a. Usual form (Kugelberg-Welander)
       b. 'Ryukyuan' form
       c. With microcephaly and mental subnormality
    2. Autosomal dominant
  - IV. Adult
    1. Autosomal recessive
    2. Autosomal dominant
    3. X-linked recessive
- *B. Distal*
  - I. Autosomal recessive
  - II. Autosomal dominant
- *C. Juvenile progressive bulbar palsy*
  - Autosomal recessive
  - I. Usual form (Fazio-Londe)
  - II. With nerve deafness (Van Laere)
- *D. Scapuloperoneal*
  - I. Autosomal dominant
  - II. Autosomal recessive
  - III. X-linked recessive
- *E. Facioscapulohumeral*
  - Autosomal dominant

* See Emery (1971, 1973).

TABLE II *Methods available for resolving heterogeneity in neuromuscular disorders*

- *A. Phenotypic (clinical)*
  1. Distribution of muscle weakness
  2. Age at onset, age at death, etc.
  3. Arthrogryposis present or absent
- *B. Biochemical*
  1. Primary
  2. Secondary, e.g. SCK
- *C. Genetic*
  1. Mode of inheritance
  2. Allelism
  3. Linkage
- *D. Abnormalities in heterozygotes*
- *E. Disease association*
  - e.g., HL-A type

ate heterogeneity in cases of congenital blindness and profound childhood deafness. ernatively one may study the offspring of a parent who is heterozygous for 2 dominant its. If the genes are allelic then individual offspring will inherit either trait but never th or neither. If, however, the genes are not allelic then individual offspring may inherit th traits, either trait or neither trait. For example, this has been reported in various moglobinopathies. Presumably because of the rarity of SMA such tests for allelism e not been reported. A possible explanation for the so-called intermediate or type II m of childhood SMA (Fried and Emery, 1971) might be that this represents a *genetic mpound* of the type I (Werdnig-Hoffmann) and type III (Kugelberg-Welander) alleles. idence for the existence of genetic compounds has been presented, for example, in the e of certain chondrodystrophies (McKusick et al., 1973).

Linkage studies between inherited marker traits and different forms of SMA might o indicate genetic heterogeneity. For example, if one form of SMA, but not another, re found to be linked to a particular marker trait this would indicate that these 2 forms SMA are fundamentally different because they are due to genes at different loci. So far re have been no reports of linkage studies involving any of the different forms of SMA. The demonstration of abnormalities in heterozygotes for one recessive form of SMA t not in heterozygotes for another would also indicate heterogeneity. Preliminary studies ggest, for example, that EMG abnormalities in the quadriceps muscle are present in both rents of children with type I SMA (Werdnig-Hoffmann) but only in mothers of children th type II SMA (Emery et al., 1973).

The *association* of different clinical forms of a disorder with different marker traits may o help resolve heterogeneity. For example, 2 different forms of myasthenia gravis have en shown to be associated with different HL-A types (Feltkamp et al., 1974). Search for ociations with HL-A types or other marker traits might therefore be a useful means of monstrating heterogeneity in SMA, but no relevant studies have been reported.

Investigations concerned with resolving heterogeneity in SMA have so far concentrated demonstrating phenotypic (clinical) and genetic differences. The fact that various ically distinct forms of SMA are inherited differently implies that they are due to genes different loci. Most of the present controversy concerning the problem of resolving erogeneity is whether in those cases where onset is before adulthood, resolution can be ieved on clinical grounds.

CLASSIFICATION BASED ON MODES OF INHERITANCE

as been assumed that SMA is inherited though it has to be recognised that within this up of diseases there may be one or more phenocopies.

As a first step in resolving heterogeneity cases must be classified according to family tory. At the simplest level they may be divided up into those where there is only one cted person in the family ('sporadic'), families where there are at least 2 affected sibs with no other affected relatives ('sibship'), and families where a parent and child are cted ('parent-child'). It is presumed that some of the 'sporadic' cases and probably st of the 'sibship' cases are the result of recessive inheritance, whereas cases in the rent-child' group are likely to be the result of dominant inheritance. A further category ther') has been used to include those families where affected individuals were second or n third degree relatives. The latter cases may be the result of dominant inheritance h reduced penetrance, recessive inheritance, or multifactorial inheritance.

In the present study the distribution of families within these various categories is shown Table III. The results suggest that the 'sibship' group does in fact represent a recessive m of SMA since 5 out of 69 (7.2%) of these families were consanguineous. Further, presumably dominant form of this type of SMA ('parent-child' group) is much less mmon than the recessive form. There was also consanguinity in 2 out of 21 (9.5%) families

TABLE III *Distribution of families according to family groupings*

	Sporadic	Sibships	Parent-child	Other	Total
Families	240	69	8	21	338
Consanguinity	0	5	0	2	7
Cases	240	138	29	37	444
Sex ratio (M/M/F)	0.54	0.59	0.55	0.59	0.56 *

* Significantly different from 0.50 ($P < 0.05$).

where more distant relatives were affected which suggests that, at least in these cases, recessive inheritance with inbreeding might be the explanation.

There would appear to be no *major* contribution by an X-linked gene to any of the groups since none of the sex ratios, for each group considered separately, differed significantly from 0.50. However, the overall sex ratio (0.56) does differ significantly from 0.50 ($P < 0.05$) indicating that boys are more commonly affected than girls.

CORRELATIONS BETWEEN RELATIVES

An idea of the nature of genetic factors in aetiology may be gained by considering correlations between relatives if there is variation in clinical symptoms or signs associated with the disease (Haldane, 1941). The expected correlations between sibs for such symptoms or signs are (*a*) zero for a major locus with random environmental effects, (*b*) up to 0.5 for a major locus with many modifying genetic factors, and (*c*) up to unity if there are 2 (or more) major loci (i.e., assuming that the variations in symptoms or signs are due to differences between these loci). In the 'sibship' group the correlation coefficients (with 95% confidence limits) for age at onset and age at death (transformed to logarithms because of their skewed distributions) were 0.77 (0.67–0.86) and 0.72 (0.47–0.87) respectively. These results suggest that in the 'sibship' group there is heterogeneity with the operation of 2 or more major genes.

CLINICAL HETEROGENEITY

Having classified patients according to their family history, the next step was to decide if there were any significant clinical differences between these groups. When *all* cases were considered together, ages at onset and ages at death were not normally distributed and therefore these results have been expressed as quartiles (Table IV). There is clearly considerable variation in age at onset. In the 'parent-child' (dominant) group affected individuals appear to survive longer, only occasionally exhibit muscle fasciculations and usually learn to sit and stand without support (Table V). It may be that the 'parent-child' (dominant) group is therefore more benign than the 'sibship' (recessive) group. However, this may be a reflection of the way in which this group was selected, which was for affected individuals who survived to reproduce and have affected children.

Clinical differences are only meaningful if there is homogeneity within families. When age of onset is plotted against age at death (or current age) for affected *sibs* (Fig. 1), it would seem that there is a definable group with onset before 6 months and in which death occurs before 2 yr of age. This is the *infantile* or type I form of SMA. Patients in this group were never able to sit without support. The data suggest that if onset is after 6 months or a child has learned to sit without support, then it is unlikely to be the infantile form of SMA.

ABLE IV *Age at onset and age at death according to family groupings*

	Sporadic	Sibships	Parent-child	Other	Total
ge at onset (months)					
Number	228	132	16	37	413
Quartiles – 1	1 *	1	3	2	1
2	6	6	13	8	6
3	12	19	21	24	15
Range	1–192	1–288	1–168	1–204	1–288
ge at death (months)					
Number	72	57	— **	15	148
Quartiles – 1	5 *	5	—	5	5
2	7	7	—	8	8
3	24	23	—	27	30
Range	1–168	1–432	—	3–576	1–576

Upper limit for 1st quartile (etc.).
Only 4 cases, ages at death being 198, 228, 324 and 780 months.

ABLE V *Clinical course according to family groupings. Results expressed as percentages*

	Sporadic	Sibships	Parent-child	Other	Total
without support *	79	89	96	85	84
od without support *	54	68	96	52	62
iculations	32	54	6	48	43
ibar involvement	51	46	31	64	50

At least at some stage in the course of the disease. Individuals who died before, or whose current ge is less than 1 yr in the case of sitting, or less than 2 yr in the case of standing, have been cluded.

Bimodality, suggesting heterogeneity may be demonstrable graphically, and provided data are normally distributed, the point of overlap ('x') may be determined from knowing means and standard deviations of the 2 groups (Penrose, 1951). It is then possible to ulate the proportion of cases which will be misclassified using the particular criterion der consideration (Figs. 2 and 3). The method is first to subdivide cases according to trait and then determine the misclassification which results when another (independent) erion is used. In the present study (excluding the infantile group) cases were divided 2 groups according to whether onset was before or after 2 yr of age since it has been gested that this may distinguish an intermediate (type II) from a juvenile (type III) m of SMA (Fried and Emery, 1971). The means and standard deviations for age at th in these 2 groups were then calculated to be 88.6 $\pm$ 63.4 (n = 29) and 423.0 $\pm$ 274.4 = 4) respectively, and therefore 'x' is 0.99 and the point of overlap in age at death is 6 + 0.99 (63.4) months or roughly 12.6 yr. From Figure 3 the proportion of cases mis-sified on the basis of age at death is about 16%. The data are very limited and the lts need to be treated with caution, but this shows how a classification by one (or more n one) trait can be tested for consistency and for agreement with other traits.

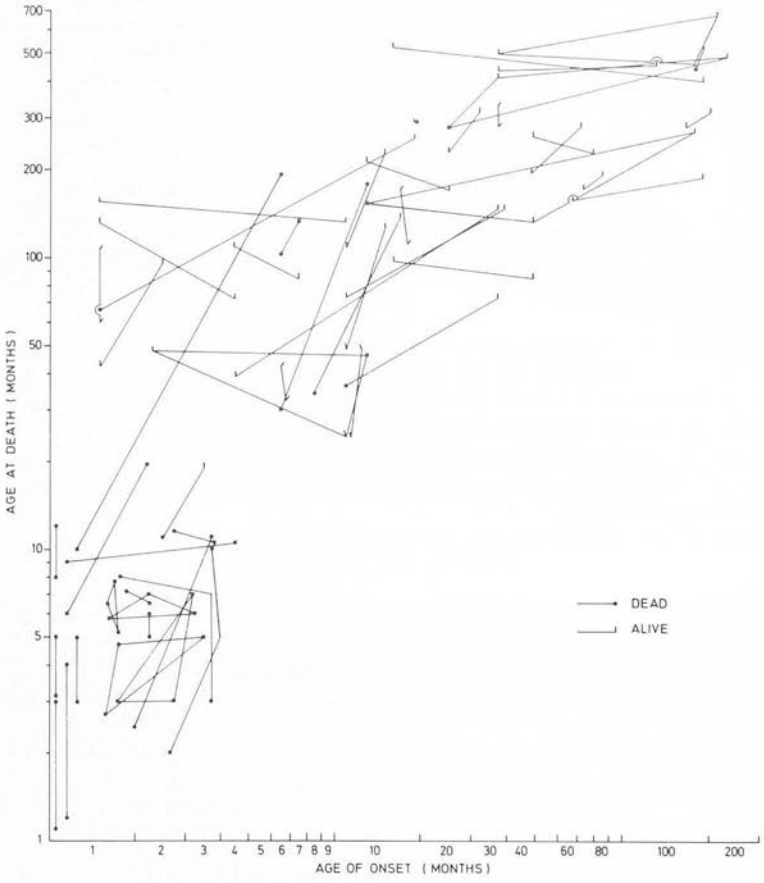

Fig. 1 Age at onset and age at death (or current age) in sibs. Connecting lines join affected individuals in each sibship.

GENETIC COUNSELLING

In general, families with several affected individuals are more likely to be ascertained and reported than families where there is only one affected individual. This has to be taken into account when calculating the proportion of affected sibs of index cases. Details of these calculations are to be found in Cavalli-Sforza and Bodmer (1971).

Assuming *truncate* selection (which gives an overestimate) the proportion of affected sibs of index cases is calculated to be 0.28 and 0.23 for infantile and non-infantile cases respectively, whereas assuming *incomplete single* selection (which gives an underestimate) the proportion of affected sibs is 0.16 for both infantile and non-infantile cases. The overall average is 0.20. Therefore the risk to sibs born subsequent to a child with proximal SMA where onset is before adulthood is roughly 1 in 5 provided there is no other family history and the parents are healthy.

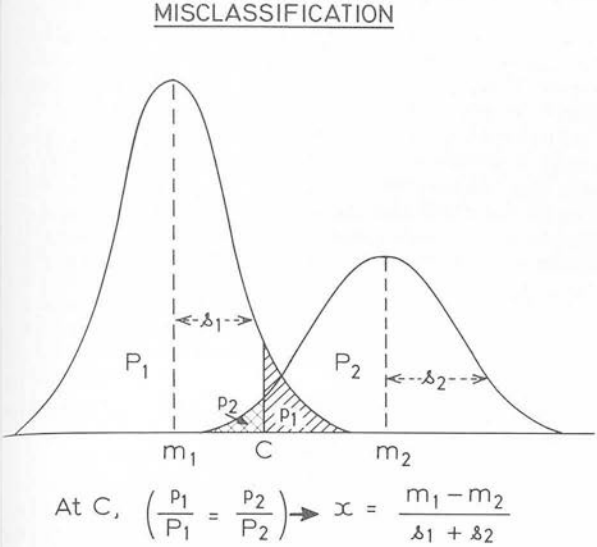

Fig. 2 Two overlapping populations, illustrating the way in which point 'x' is determined.

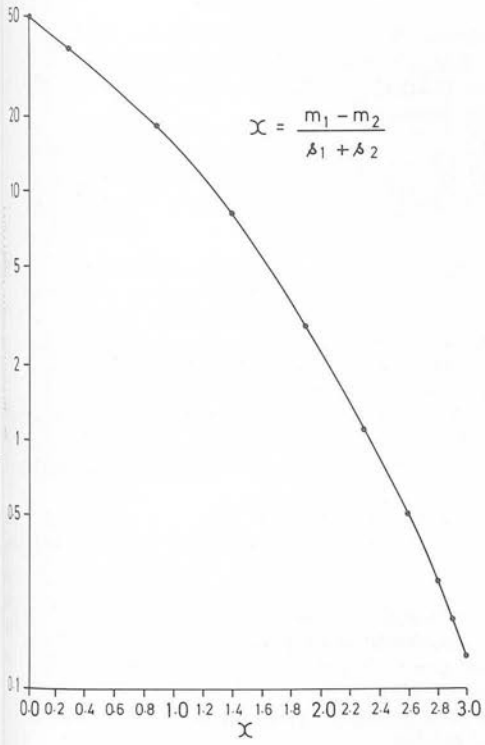

Fig. 3 Percentage misclassification for various values of 'x'.

SUMMARY AND CONCLUSIONS

The spinal muscular atrophies are a heterogeneous group of disorders. There is general agreement regarding the existence of several clearly definable forms of SMA where the predominant muscle weakness is non-proximal. However, in the case of proximal SMA with onset before adulthood, there is some controversy. Methods for resolving heterogeneity in this latter group of disorders have been briefly reviewed and illustrated using data from the more recent literature as well as from material collected in this Department. It would seem that a dominant form exists which is much less common and possibly more benign than recessive forms. The latter can be further subdivided into 2 and possibly 3 different types on the basis of certain clinical criteria. However, because of variations between authors, analysis *within* authors with subsequent pooling of results would perhaps be more meaningful. The present data were not sufficient for such an analysis but this may be possible with the more extensive data from the international collaborative study.

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APPENDIX

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DISCUSSION

Dyck (Minnesota, U.S.A.) expressed doubts about the value of this type of collaborative dy because the standards and criteria of diagnosis were not uniformly reliable. *I. Hausmanowa-Petrusewicz (Warsaw, Poland)* advised caution in the use of 'age at onset' as a parameter in an sidiously progressive disease. *J.B. Peter (California, U.S.A.)* advised the use of multidimensional lysis of the data.

ry (subsequent written reply) In answer to Dr. Dyck's doubts about the value of collabora- studies, many of the difficulties inherent in such studies, due to variations in reporting, may be come by doing genetic analyses within authors, with subsequent pooling of results. With a e amount of data (as may be available in the collaborative study) such analyses will be possible the results therefore more meaningful. Regarding variations in age at onset, we accept that may not be the most reliable parameter but our studies so far have clearly shown that there is gh degree of statistically significant intrafamilial correlation of age at onset. Again analysis in and between families will be helpful. Certainly Dr. Peter is right when he suggests that a tidimensional analysis is probably necessary and this we hope to achieve.

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in Great Britain

Statistical resolution of genetic heterogeneity in familial disease

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The multifactorial model of disease liability with a threshold (Falconer, 1965) had proved useful in summarizing data on the frequency of a familial disease in the population and in relatives of affected individuals. The model has proved robust in practice as a descriptive tool and has been widely applied. It has also been used to derive expectations to test the fit to observed or simulated data (Smith, 1971*a*; Krüger, 1973) and to calculate recurrence risks in relatives for a disease (Curnow, 1972; Mendell & Elston, 1974; Smith, 1971*b*). As used so far, the model may well serve to obscure heterogeneity of different genetic forms of a disease by lumping together data on similar clinical groups, in order to derive a single summarizing statistic, the heritability of liability, for the disease.

However, the multifactorial model also can be used to resolve genetic heterogeneity in a disease by testing whether any splitting of the disease is valid. If the disease can be split into two (or more) groups, on any criterion, we can test if the groups are genetically distinct and if so we can measure the 'genetic correlation' (Falconer, 1960, 1967) between their liabilities. The data required are simply the frequencies of the two groups of disease in the relatives of the probands of each of the two groups.

Before making any genetic interpretations of such data it is important to remove or discount for common familial environment effects among relatives. This may be done by also considering relatives living apart or unrelated individuals living together. In this paper it is assumed that such groups have already been removed or discounted. We shall use the term *group* for a phenotypic grouping of the disease and use the term *form* to represent a genetic class. For simplicity, I will consider only first degree relatives. A summary of the notation used is given as an appendix.

SIMPLE TESTS

Suppose a familial disease can be divided (on any criteria) into two groups 1 and 2. Observed data on the population frequency for the two groups and on the frequencies of the two groups in relatives will be of the kind shown in Table 1. That is P_1 and P_2 are the population frequencies of disease groups 1 and 2 respectively. Among probands, with disease group 1 there will be N_1 relatives, of whom A_{11} will be affected with disease group 1 and A_{12} with disease group 2. P_{12} is then the *conditional* probability ($= A_{12}/N_1$) that a relative of a proband with disease group 1 will be affected by disease group 2, and similarly for P_{11}, P_{21} and P_{22}.

A simple test for genetic identity between the two disease groups can be made by a 2×2 chi-square of the number of affected relatives (A-values in Table 1). For example, consider the data in Table 2 on spina bifida and anencephaly from Carter and co-workers (1968, 1973). In both

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Table 1. *Form of data on probands and on their relatives for two disease groups*

Proband group	Population frequency	Affected relatives: Group 1 Number	Affected relatives: Group 1 Proportion	Affected relatives: Group 2 Number	Affected relatives: Group 2 Proportion	All relatives
1	P_1	A_{11}	P_{11}	A_{12}	P_{12}	N_1
2	P_2	A_{21}	P_{21}	A_{22}	P_{22}	N_2

Table 2. *Anencephaly and spina bifida in first degree relatives of probands for each of these disorders*

Proband	Population frequency (%)	No. affected relatives: Anencephaly	No. affected relatives: Spina bifida	Total relatives
(*a*) Carter, David & Laurence, 1968				
Anencephaly	0·36	16	13	707
Spina bifida	0·42	20	32	854
(*b*) Carter & Evans, 1973				
Anencephaly	0·13	24	17	754
Spina bifida	0·17	12	13	730

(*a*) $X_1^2 = 1{\cdot}47$; (*b*) $X_1^2 = 0{\cdot}32$.

sets of data, the chi-squares were small and so the liabilities to the two diseases must be very closely genetically correlated with one another.

Similarly, we can test for lack of any genetic correlation between the two groups. If there is no genetic correlation in liability the proportions P_{12} and P_{21} in Table 1 should equal the population frequencies P_2 and P_1 respectively. Usually the expected numbers (N_1P_2 and N_2P_1) will be small if the disease is rare so a chi-square may be inappropriate. An alternative is to use the Poisson distribution for the rare events. Given the expected number, the probability of getting the observed number by chance can be read off from tables of the distribution (e.g. Table 7, *Biometrika Tables*, Pearson & Hartley, 1954). For example in the first row of Table 2, if the conditions are genetically distinct, the expected number of relatives with spina bifida for probands with anencephaly is $0{\cdot}0042 \times 707 = 2{\cdot}97$. With this mean (and variance) the probability of obtaining 13 or more affected relatives by chance is less than 0·1 % and similarly for the other rows. Of course with these diseases the hypothesis that they are distinct genetic forms is thoroughly rejected.

These simple methods provide the basis for resolving genetic heterogeneity in familial disease. If there are distinct genetic forms of the disease, then these are likely to differ in several respects (clinical, biochemical, physiological or statistical). Thus more detailed study of a disease should lead to splitting into groups whose genetic similarity or distinctness can be tested by the simple methods outlined above and any genetic heterogeneity should be detected. Lack of resolution may be due to inaccurate grouping of the disease and other groupings should be tried and tested. Of course this is the way that clinicians have empirically investigated and resolved many heterogeneous familial diseases in the past. Similarly, for those familial diseases which are currently unresolved, a systematic procedure of grouping and testing should be effective in detecting any genetic heterogeneity that exists.

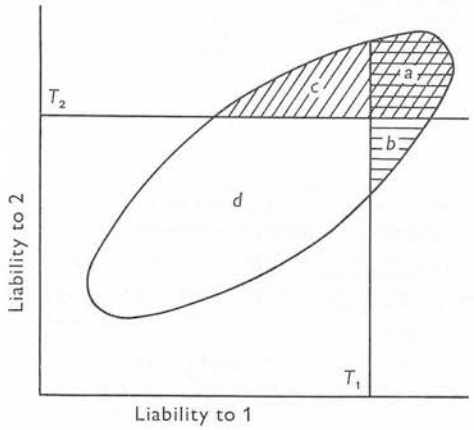

Fig. 1. The bivariate phenotypic distribution of liability to two disease forms (1 and 2), with thresholds (T_1 and T_2) and segments cut off (a, b, c, and d).

Table 3. *Matrix of phenotypic correlations in liability to two disease forms among relatives*

Individual		Relative	
Form 1	Form 2	Form 1	Form 2
1	r_{12}	r_{11}	r^*_{12}
r_{12}	1	r^*_{12}	r_{22}
r_{11}	r^*_{12}	1	r_{12}
r^*_{12}	r_{22}	r_{12}	1

CORRELATED LIABILITIES

There are many familial diseases where heterogeneity is suspected but different genetic *forms* ve not been resolved, perhaps because of some overlap between different disease groupings. example, there may be overlap in liability between early and late onset diabetes or in bility to the different clinical forms of schizophrenia. In practice the simple cases without over- will already have been resolved and it will be the intermediate cases that need further stigation. That is, a major reason for lack of resolution for some familial diseases may be ause the liabilities of the different disease forms are correlated, both phenotypically and etically.

With two correlated disease forms 1 and 2, the univariate multi-factorial model (Falconer, 5) becomes a bivariate normal as in Fig. 1. One threshold (T_1) applies to form 1 on one co- linate, and the other (T_2) to form 2 on the other co-ordinate. Extending the model to include atives, the problem becomes one of dealing with truncation of a 4-way multivariate normal tribution of liabilities to forms 1 and 2 in individuals and in their relatives. The parameters of distribution can be summarized by a symmetric 4×4 phenotypic correlation matrix, as in ble 3. The parameters r_{11} and r_{22} are the correlations among relatives for liabilities to forms 1 2 respectively, r_{12} is the phenotypic correlation in liability between forms 1 and 2 within viduals and r^*_{12} is the correlation in liability between forms 1 and 2 for an individual and a tive. The other two parameters are the threshold points T_1 and T_2, imposed by truncation by threshold, giving six parameters in all.

Table 4. *Correlation in liability between 1st degree relatives for a disease which combines two genetically uncorrelated diseases 1 and 2*

Correlation in liability for 1st degree relatives		Proportion of disease 1, $(\bar{P}_1/P)$		
Disease 1 (r_{11})	Disease 2 (r_{22})	0·1	0·5	0·9
0·0	0·2	0·18 (0·18)*	0·09 (0·10)	0·01 (0·02)
	0·4	0·37 (0·36)	0·23 (0·20)	0·04 (0·04)
0·2	0·0	0·01 (0·02)	0·09 (0·10)	0·18 (0·18)
	0·2	0·18 (0·20)	0·15 (0·20)	0·18 (0·20)
	0·4	0·37 (0·38)	0·26 (0·30)	0·20 (0·22)
0·4	0·0	0·04 (0·04)	0·23 (0·20)	0·37 (0·36)
	0·2	0·20 (0·22)	0·26 (0·30)	0·37 (0·38)
	0·4	0·38 (0·40)	0·34 (0·40)	0·38 (0·40)

Population frequency (P) = 1%, $r_{E_{12}} = 0$. * ( ), weighted average of r_{11} and r_{22}.

The correlations can be interpreted genetically if common familial environmental effects are discounted as already discussed. The phenotypic correlations are then $r_{11} = \frac{1}{2}h_1^2$, $r_{22} = \frac{1}{2}h_2^2$ and $r_{12}^* = \frac{1}{2}h_1 h_2 r_{G_{12}}$ (Falconer, 1960), where h_1^2 and h_2^2 are the heritabilities of liabilities and $r_{G_{12}}$ is the genetic correlation in liability between the two forms. For r_{12} a term for common environmental factors affecting the two disease forms in the same individual must be included so that

$$r_{12} = h_1 h_2 r_{G_{12}} + \sqrt{[(1-h_1^2)(1-h_2^2)]}\, r_{E_{12}}$$

(Falconer, 1960), where $r_{E_{12}}$ is the correlation due to environmental effects (assuming no correlation of genotype and environment) (Table 4).

INDEPENDENT DIAGNOSIS

If there is independent ascertainment and diagnosis of the two forms of the disease, individuals with both forms (that is above both thresholds T_1 and T_2) will be identified as such. Thus the proportions falling into the four segments a, b, c and d in Fig. 1 will be known, and similarly for the relatives. In Table 1, P_i (the population frequency for disease group i) is then the frequency of probands ascertained for disease form i (irrespective of form j). Similarly, P_{ij} (the frequency of group j in relatives of probands with group i) is the frequency of form j (irrespective of form i) in relatives of probands with form i (irrespective of form j). The parameters of Table 3 can be estimated from these observed P frequencies by the original Falconer (1965) method. Let x_i and a_i (distinguished from the a in Fig. 1 by the subscript) be respectively the deviate at the threshold and the average deviate associated with population frequency P_i of disease group i, and similarly for x_{ij} and a_{ij} associated with the P_{ij}. Then calculate

$$R_{ij} = \frac{(x_j - x_{ij})}{a_i}$$

or more precisely (Reich, James & Morris, 1972)

$$R_{ij} = \frac{x_j - x_{ij}\sqrt{[1-(x_j^2-x_{ij}^2)(1-x_i/a_i)]}}{a_i + x_{ij}^2(a_i - x_j)}.$$

R_{11} and R_{22} are estimates of $r_{11} = \frac{1}{2}h_1^2$ and of $r_{22} = \frac{1}{2}h_2^2$ respectively and from these we can h_1, h_2. The R_{12} and R_{21} are both estimates of $R_{12}^* = \frac{1}{2}h_1h_2r_{G_{12}}$, so G_{12} the Falconer (1967) imate of $r_{G_{12}}$ can be derived.

NON-INDEPENDENT DIAGNOSIS

Usually in practice the ascertainment and diagnosis of two correlated disease forms will not independent, one often precluding the other. For example, diagnosis of anencephaly will preude diagnosis of spina bifida, and cases with early onset diabetes cannot also have late onset. individuals with both forms 1 and 2 of a disease fall partly into group 1 and partly into group hen the true population frequencies of the two forms will be underestimated, and so any imates of parameters derived from them will be biased. The main purpose of the rest of the per is to assess the extent of these biases and to develop methods to adjust for them in analysis. The problem arose in trying to resolve the genetic relation of early onset and late onset abetes (Smith, Falconer & Duncan, 1972). Two extreme models were tested, (1) that the late set individuals are those lying between a low and a high threshold on a common univariate stribution of liability to diabetes and (2) that the liabilities for early and late onset disease re uncorrelated. Neither model fitted the data well, though the former was preferred, and an ermediate form of analysis was suggested.

If individuals in segment (a) in Fig. 1 are not diagnosed with both disease forms 1 and 2 they ay fall either into group 1 or into group 2. Since we do not know the grouping in practice we ll deal with the two extreme cases which should cover the intermediate cases. One extreme se will be when all of segment (a) falls into group 1. The quantities in Table 1, in terms of the gments in Fig. 1, now become

	Segment(s) for relatives	given	Segment(s) for proband
P_{11}	$(a+b)$		$(a+b)$
P_{12}	c		$(a+b)$
P_{21}	$(a+b)$		c
P_{22}	c		c
P_1	—		$(a+b)$
P_2^*	—		c

ese conditional probabilities (P_{ij}) can be estimated by the numerical methods to be described d can then be compared with observed data. Since either disease group can be coded 1, the alysis can be repeated interchanging the disease groups, that is letting segment (a) fall into oup 2.

METHODS

The analysis of disease forms with independent diagnosis and ascertainment was described fore. The methods which follow deal with non-independent diagnosis and ascertainment and th the grouping described in the previous section. In practice we observe the (P_{ij}) conditional equencies (of disease group (j) in relatives of probands with disease group (i)) and wish to imate the true (r_{ij}) parameters for the forms of the disease. Here we first develop methods to the reverse, namely to estimate the (P_{ij}) frequencies given the (r_{ij}) parameters. We can then amine what effects the different groupings of the disease forms have on the (P_{ij}) frequencies, d on the Falconer (1965, 1967) estimates of heritability and genetic correlation derived from

the (P_{ij}). We can also then use the methods iteratively to estimate the (r_{ij}) parameters which give the best fit to a set of observed (P_{ij}) frequencies.

Given a set of parameters P_1, P_2, r_{11}, r_{22}, r_{12} and r_{12}^* as in Tables 1 and 3, it is possible to derive the conditional frequencies P_{11}, P_{12}, P_{21} and P_{22} for the 4-variate normal distribution. This was done in two ways. The first was by numerical integration, as follows. The frequency in any cell of the 4-variate normal distribution can be numerically evaluated from the distribution formula (e.g. Mood & Graybill, 1963). For each P_{ij} we can identify (as given in the previous section) the segments $(a+b)$ or c for relatives, and similarly for probands, as cut off by the thresholds T_1 and T_2 in Fig. 1. The segments cut off were subdivided into a grid of 100 equal squares, both for relatives and for probands, giving 10^4 cells in all. The frequencies in these cells were then evaluated and accumulated to get the unconditional frequency F_{ij} for each proband-relative combination. The unconditional frequency F_i for a proband segment alone was evaluated in the same way but allowing the grid for relatives to cover all segments a, b, c and d. These unconditional frequencies were then used to get the conditional frequencies (P_{ij}) as

$$P_{ij} = F_{ij}/F_i.$$

To check on the results derived in this way and to get a solution involving less computing time, a second method was also used. This was the approximate method proposed by Mendell & Elston (1974) for deriving recurrence risks with the multifactorial model. The solution depends on formulae by Aitken (1934) for parameters of a multivariate normal distribution after selection of one of the variables. Several selected variables can be treated in turn. The approximation introduced by Mendell & Elston was to consider the truncated distribution as if it were normal, and they showed that this had only a small effect on the results obtained. Let u refer to probands and v to their relatives. The method gives conditional probability terms like Prob $(v_1|u_1) = P_{11}$ and Prob $(v_2|v_1, u_1)$, the probability that a relative has disease *form* 2, given that he also has disease *form* 1 and the proband has disease *form* 1. The values of the (P_{ij}) can be derived from these, for example

$$P_{12} = \frac{\text{Prob } (v_2|u_1) - \text{Prob } (v_1|u_1)\ P(v_2|v_1, u_1)}{1 - \text{Prob } (v_1|u_1)},$$

which is the conditional probability that relatives have disease *group* 2 given that probands have disease *group* 1. The computer program to estimate the P_{ij} in this way is available on request.

With these procedures we can examine what effects the different groupings of the disease forms have on the P_{ij} frequencies and on the R_{ij} correlation estimates derived from them by the original Falconer (1965) method. The observed disease group frequencies will be P_1 and P_2^* $(= P - P_1)$ in the population and P_{11}, P_{12}, P_{21} and P_{22} in their relatives. The R_{ij} were derived using formula (2). R_{11} and R_{22} are estimates of parameters r_{11} and r_{22} respectively, but R_{22} will be biased because of truncation on disease group 1 in the population and in relatives. From R_{12} and R_{21}, the Falconer (1967) estimates of the genetic correlation $r_{G_{12}}$ are derived as

$$G_{12} = \frac{R_{12}}{\sqrt{[R_{11}\, R_{22}]}} \quad \text{and} \quad G_{21} = \frac{R_{21}}{\sqrt{[R_{11}\, R_{22}]}}.$$

Knowing the true values of the parameters and the estimates derived after grouping the disease forms, the biases in the estimates (R_{22}, G_{12} and G_{21}) can be assessed.

We can also use the procedures for deriving P_{11}, P_{12}, P_{21} and P_{22} to estimate the r_{11}, r_{22}, r_{12} and r_{12}^* for a given set of observed data. The fit to the data by the model with a given set of (r_{ij}) parameters can be assessed by a Goodness of Fit chi-square of the expected and observed numbers (A_{ij}) of affected relatives. A serial search procedure to find the parameter values giving the minimum chi-square was used following Reich, James & Morris (1972) to get the best estimates of the r_{ij} parameters. In practice several of the parameters (P, P_1 and r_{11}) could be taken as fixed and so the searches were usually only over the other three parameters. The procedure can then be repeated with the disease groups interchanged to find which grouping gives the best fit to the data.

RESULTS

First the two methods for deriving the frequencies P_{11}, P_{12}, P_{21} and P_{22} were compared. For each method, the total population frequency (P), the frequency of disease form 1 (P_1), the true correlations (r_{11} and r_{22}) in liability among relatives for form 1 and form 2 respectively, and the correlations (r_{12} and r_{12}^*) of liability for form 1 with liability for form 2 in the same individual and across relatives were given. The observed frequency of group 2 is $P_2^* = P - P_1$. The true frequency of form 2, needed to find the threshold T_2, was first derived by numerical integration, given P, P_1 and r_{12}. The computer programs then went on to derive P_{11}, P_{12}, P_{21} and P_{22}. From these the correlation estimates R_{11}, R_{12}, R_{21} and R_{22} were derived corresponding to the correlations which would be estimated from an observed set of data, as in Table 1. The two methods gave very similar correlation values, usually equal to two decimal places, but with differences gradually increasing as the population frequency decreased due to the coarseness of the numerical integration classes. Because the approximate matrix method showed less deviation from the expected values (for R_{11}) and took only about one twentieth of the computing time of the other, it was used for all the subsequent calculations.

Since form 1 results from the first truncation, $R_{11} = r_{11}$. The results for R_{22} and for the genetic correlation values (G_{12} and G_{21}) derived from R_{12} and R_{21} are given in the top and bottom rows of Table 5. The correlation (R_{22}) in liability for group 2 may be appreciably lower than the true value r_{22} (0·2 or 0·4). However, the genetic correlation values G_{12} and G_{21} are high and vary about unity, their true value. Thus despite the biases due to truncation, the Falconer genetic correlation estimates will still tend to show up the true genetic relation between two groups of the same disease. When the two groups are disproportionate, the values in Table 5 vary rather more, but the same general conclusions hold.

Another possibility is that two disease forms may arise from the same genetic distribution but are different because of different environmental factors which may, or may not, be correlated. The correlations in liability (r_{11} and r_{22}) may then be different in the two diseases and the correlation $r_{12} = h_1 h_2 + \sqrt{[(1-h_1^2)(1-h_2^2)]}\, r_{E_{12}}$. The results are given in the two middle rows of Table 5 and are similar to those discussed above.

CORRELATED GENETIC LIABILITIES

If the two disease forms have genetically correlated liabilities ($0 < r_G < 1$), we can use the same methods to derive the Falconer genetic correlations G_{12} and G_{21} and compare them with the true value $r_{G_{12}}$. A series of examples were run and the results were similar to those described in Tables 4 and 5. The value for R_{22} consistently underestimated the parameter r_{22}, but the values

Table 5. *Estimate of parameters for two disease forms with the same genetic liability distribution but with different environmental factors which may be correlated* ($r_{E_{12}}$).

Above: Estimate (R_{22}) of correlation (r_{22}) in liability between relatives for group 2.
Below: Estimates (G_{12}, G_{21}) of the genetic correlation (r_{G12}) between forms 1 and 2.

Correlation in liability for 1st degree relatives		Proportion allocated to disease 1, (P_1/P)					
		0·1		0·5		0·9	
		r_{E12}		r_{E12}		r_{E12}	
Form 1 (r_{11})	Form 2 (r_{22})	0	1·0	0	1·0	0	1·0
0·2	0·2	0·19	0·18	0·18	0·14	0·17	0·17
		1·22 0·84	1·21 0·84	1·01 0·98	1·02 0·96	0·87 1·19	1·11 0·77
0·2	0·4	0·39	0·39	0·37	0·40	0·35	0·42
		0·94 0·80	0·94 0·80	1·01 0·99	1·01 0·99	0·82 1·39	0·77 0·96
0·4	0·2	0·18	0·16	0·15	0·08	0·13	0·04
		1·37 0·78	1·19 0·75	0·99 0·95	0·77 0·70	0·83 1·21	0·71 1·32
0·4	0·4	0·36	0·36	0·30	0·27	0·25	0·26
		0·93 0·74	0·93 0·74	1·01 0·97	1·02 0·95	0·80 0·95	0·97 0·98

Population frequency 1 %, $r_{G12} = 1{\cdot}0$.

of G_{12} and G_{21} again varied about $r_{G_{12}}$ and gave a good indication of the true genetic correlation. Since we have dealt with the most extreme situations in these sections ($r_E = 0$, or 1, and all of segment (a) in group 1), the deviations of the Falconer estimates from the parameters will usually be much less than those shown in Tables 4 and 5.

APPLICATION

Evaluation of the proportions P_{11}, P_{12}, P_{21} and P_{22} for different parameter sets allows the testing of hypotheses about two disease forms. In addition we can derive estimates of the parameters which give the best fit to a set of data by iterating to find the minimum chi-square. As an example, the genetic relation of early onset (E) and late onset (L) diabetes is examined using these methods. Data from Smith, Falconer & Duncan (1972) are presented in Table 6. The estimates of correlation in liability for early onset, late onset and all diabetes were 0·38 ± 0·03, 0·30 ± 0·02 and 0·29 ± 0·02 respectively. The two Falconer estimates of the genetic correlation are 0·24 ± 0·07 and 1·04 ± 0·05, differing markedly from one another. The difference does not seem to be entirely due to differential mortality of diabetics as was first implied (Darlow, Smith & Duncan (1973)). The hypotheses (1) that there is a single genetic liability to diabetes ($r_G = 1{\cdot}0$) and (2) that early and late onset are two independent genetic disorders ($r_G = 0{\cdot}0$) were tested but both could be rejected by the data. However, if we consider early and late onset as two genetic forms, each with their own correlation in liability (or heritability) and with a genetic correlation between them, we can find by iteration an adequate fit to the data. This indicates a considerable genetic overlap in the early and late onset forms of the disease with a genetic correlation of 0·65 in their liabilities.

The hypothesis of a single disease liability was also tested in the data on spina bifida and anencephaly in Table 2. The four genetic correlation estimates obtained by the Falconer method

Table 6. *Analyses for early and late onset diabetes*

(Data from Smith, Falconer & Duncan (1972)).

Proband	Population frequency (%)	First degree relatives: Early onset (under 25)	First degree relatives: Late onset (25 and over)
	(*a*) Frequencies		
Early onset (E) (under 25)	0·064	22/1075	36/766
Late onset (L) (25 and over)	0·912	11/6326	303/5777

(*b*) Correlation estimates

$r_{EE} = 0{\cdot}38 \pm 0{\cdot}03$ $\quad r_{G_{EL}} = 0{\cdot}24 \pm 0{\cdot}07$

$r_{LL} = 0{\cdot}30 \pm 0{\cdot}02$ $\quad r_{G_{LE}} = 1{\cdot}04 \pm 0{\cdot}05$

$r_{\text{combined}} = 0{\cdot}29 \pm 0{\cdot}02$

(*c*) Parameter values fitted

Hypothesis tested	r_{EE}	r_{LL}	$r_{G_{EL}}$	r_{EL}	Goodness of Fit: X^2	df	P
One genetic disease, no environmental correlation	0·29	0·29	1·00	0·58	34·1	3	$< 0{\cdot}001$
One genetic disease, complete environmental correlation	0·29	0·29	1·00	1·00	34·8	3	$< 0{\cdot}001$
Separate genetic forms no environmental correlation	0·38	0·30	0·00	0·00	124·5	2	$< 0{\cdot}001$
Separate genetic forms complete environmental correlation	0·38	0·30	0·00	0·65	196·6	2	$< 0{\cdot}001$
Correlated genetic forms correlated environmental effects	0·38	0·30	0·65*	0·85*	3·4	2	NS

* Obtained by iteration for minimum X^2.

were 0·92, 0·71, 0·90 and 0·95 with a pooled value of $0{\cdot}87 \pm 0{\cdot}10$. This indicates that the two diseases are either genetically the same or that their genetic liabilities are very closely correlated. The data of the second study (Carter & Evans, 1973) are indeed compatible with the hypothesis that anencephaly and spina bifida are differing manifestations of a single genetic disorder, with anencephaly being the more severe group. However, the data in the second study only satisfy the hypothesis of a single liability to these diseases if spina bifida is taken as the more severe group, as is unlikely. These different results arise from the quite different patterns in the frequencies in the data from the two studies which are hard to reconcile.

DISCUSSION

Genetic heterogeneity has been demonstrated recently in many unifactorial clinical disorders. An important and intriguing question is whether there is also genetic heterogeneity in many of the common 'multi-factorial' familial disorders. The methods given here can be used to answer this question. It is reasonable to expect that if there are separate genetic forms grouped together

and considered as one clinical disorder, then those different forms are likely also to differ in many respects and properties (clinical, pathological, biochemical, statistical, etc.). Thus, if there is genetic heterogeneity, more detailed study of the disorder should lead to possible splitting into various groups. The adequacy of the criteria for splitting and the genetic identity of the groups formed can then be tested by the methods studied here. A systematic search for distinct groups is proposed as a powerful tool in resolving any genetic heterogeneity in familial diseases.

However, in practice we may have to deal less with distinct genetic groups (since many of these will already have been resolved) and more with different disease forms which have overlapping, genetically correlated liabilities, such as the different clinical forms of schizophrenia. Thus we can use the conventional method of Falconer (1967) to estimate the genetic correlation in liability between the two disease forms. What we have shown here is that even if the two disease forms overlap and are partly confounded (e.g. one precluding the other) then the Falconer method can also be applied. Thus the derived estimates, over a wide range of situations, neither consistently underestimate or overestimate the true value of the genetic correlation (Table 5) but vary around it. So it is concluded that in most cases the Falconer method is unlikely to seriously mislead the investigator in assessing the true genetic association between two diseases or two forms of one disease.

In estimation the Falconer method may well be preferred, for the more complex iterative methods derived here involve additional assumptions and approximations. Moreover, there will be other factors to take into account such as differences in frequency between sexes or generations, differences in severity, errors in diagnosis and classification and so on. The effects of such factors on the parameter estimates are likely to be larger than those studied here and they can be most readily accommodated by the Falconer method of analysis.

SUMMARY

If a disease can be split into two or more groups on any criterion (clinical, biochemical, physiological or statistical) then the grouping can be tested to establish if genetically independent forms of the disease have been identified. The data required are simply the frequencies of the two disease groups in relatives of probands for each of the disease groups. A systematic search for such distinct groups is proposed in searches for genetic heterogeneity in familial diseases.

In disease forms with overlapping, correlated genetic liabilities, the method of Falconer (1967) can be used to estimate the genetic correlation. However, when the groupings of the disease are confounded (such as one form precluding the other as in early and late onset diabetes) Falconer's method will be biased. Special methods of analysis to estimate the genetic parameters have been developed and are presented here. However, even when the groupings are confounded the Falconer method still gives reasonable estimates of the genetic correlation, in that they are unlikely to seriously mislead the investigator in the analysis and interpretation of observed data. In practice Falconer's simple method may be preferred to the more complex methods developed here because it involves fewer assumptions and can be applied over a wider range of circumstances.

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APPENDIX

Notation

	population frequency for the familial disease
	population frequency for disease form i
	liability threshold for disease form i
	number of relatives for probands with disease group i
	A_{ij}/N_i proportion of relatives within disease group j in N_i
b, c, d	segments of the bivariate distribution cut off by T_1 and T_2, see Fig. 1.
	correlation in liability among relatives for disease form i
	correlation in liability within individuals between disease forms i and j
	correlation in liability among relatives between disease forms i and j
	heritability of liability to disease form i
	genetic correlation in liability between disease forms i and j
	environmental correlation in liability between disease forms i and j
	Estimate of the correlation in liability among relatives for disease group i using text formula (2)
	Estimate of the correlation in liability among relatives between disease groups i and j using text formula (2)
	Falconer (1967) estimate of the genetic correlation in liability between disease groups i and j.

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Population structure of Barra (Outer Hebrides)

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Development of methods to predict and estimate kinship have outpaced their application (Morton, 1973). Only a few populations have been investigated in two or more ways, yet agreement among different approaches is the only way to validate the assumptions of kinship analysis. We therefore welcomed an opportunity to examine Barra, the southernmost isles of the Outer Hebrides in Scotland (Fig. 1). This population was chosen because of its degree of isolation inferred from geographic, religious, and linguistic factors. In this paper we report a study of the population structure of Barra based on an analysis of demographic variables: surname concordance (isonymy), migration, and genealogy. Bioassay of kinship from genetic and chromosomal polymorphisms will be presented subsequently. For the methods of analysis used in this paper see Morton *et al.* (1971*b*), Morton (1973).

HISTORICAL DEMOGRAPHY

The Outer Hebrides have probably been settled by agricultural man for about 4000 years (Murray, 1966). Although the report of a Roman expedition and later Norse sagas suggest that in the past (as now) many of its islands were uninhabited, there is no evidence of any discontinuity in the occupation of the larger islands. The Census returns since 1801, supported by earlier estimates of travellers and ecclesiastics, indicate a population in excess of 1000 for the past 300 years (Table 1). Less reliable accounts of 200 or more fighting men in the sixteenth century suggest that the population has not been less than 1000 for at least five centuries (Mackenzie, 1903; Campbell, 1936). From 1745 to 1911 the number of inhabitants doubled, despite emigration due to disruption of the clan system in the eighteenth century, collapse of the kelp industry after the Napoleonic wars, potato famine in the late 1840's, and clearances in favour of sheep from 1851 onwards (Table 2). During this time births in Barra were an order of magnitude more frequent than marriages, testifying to loss of the unmarried through emigration, mostly to Glasgow and Canada. The high rate of population increase has been attributed to the greater productivity of potatoes than of barley and oats, reduction of mortality by vaccination, and the development of commercial fishing and extraction of salts from seaweed. During the middle of the last century there was deliberate introduction of Protestant servants and tenants as a foil to the Catholic inhabitants. The proportion of Protestants fell during the depopulation which accompanied decline of commercial fishing in this century, and Barra remains one of the few predominantly Catholic areas in Scotland. Gaelic is commonly spoken, and these religious and linguistic factors reinforce its relative geographic isolation. However, since the population has never been small in historical times, and the seas around the Hebrides

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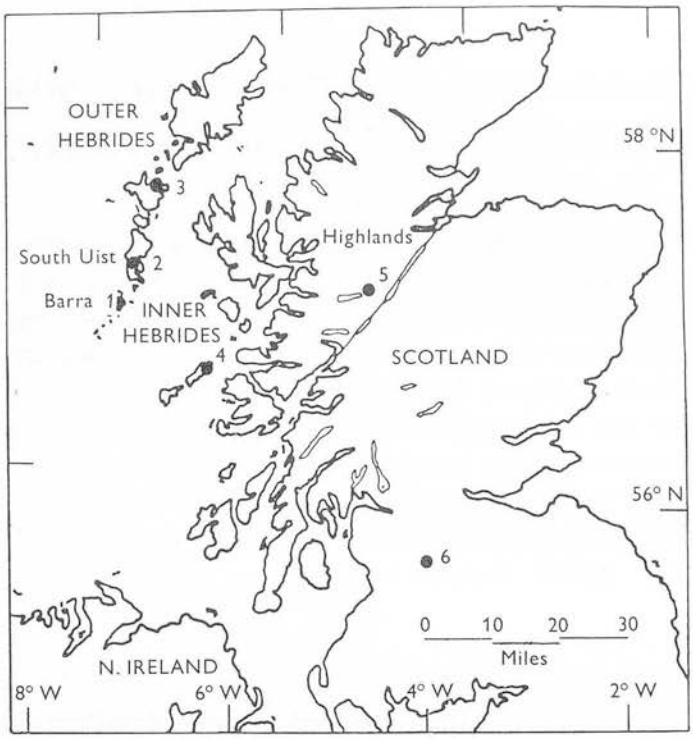

Fig. 1. Map of Scotland showing Barra and the areas chosen for isonymy and migration analysis.

Table 1. *Population of Barra (after Campbell, 1936)*

Year	Number	Year	Number
1671	1000	1791	1604
1750	1285	1851	1873
1755	1150	1911	2620
1771	1395	1972	1232

are not a formidable barrier to oarsmen, we should not expect as much inbreeding as may occur in more isolated populations, such as coral atolls or Melanesian villages (Morton, 1974).

Despite the hazards of extrapolation and the irregularities of the fluctuations, it is tempting to fit the population estimates of Table 1 to the equation

$$N_t = N_0 e^{bt}$$

where N_0 is the number of neolithic founders and t is the number of years since the population was settled by agriculturalists (Morton *et al.* 1972). For t = number of years since 2000 B.C., the least squares estimates are $\hat{N}_0 = 100$ and $\hat{b} = 0{\cdot}0007$, corresponding to a doubling time of $(1n\ 2)/b = 990$ years. From Table 1 we may reasonably take 1400 as a reasonable approximation to the census size throughout the past five centuries.

Infant mortality and emigration of the unmarried tend to lengthen generation time. In the genealogy since 1775 the mean difference in year of birth between parents and fertile children was 38 years for fathers and 33 years for mothers, declining about 5 years per century. This is clearly not an equilibrium situation. We use below a figure of 30 years as a good approximation to the generation time over the last two centuries.

Table 2. *A Barra chronology*

2000 B.C.	Neolithic chambered cairns
100 B.C.–400 A.D.	Celtic duns, brochs, and wheelhouses
800–1266 A.D.	Norse raids and occupation
1309	Barra granted to McAllen by Bruce
1372	Possession passed to Lord of the Isles
1427	Barra and Boisdale granted to McNeil
1589	McNeil raided Ireland
1601	McNeil expelled from Boisdale
1752	Potato introduced
1765–1815	Kelp industry
1846	Potato famine
1851	Clearances
1911	Decline of fishing and population

MATERIAL

The basic set of data used for this study was obtained from the civil registers of births and marriages held by the Registrar General for Scotland. Each birth entry contains the name, date and place of birth, as well as the names of both parents (including mother's maiden name) and the date and place of their marriage. The marriage record contains the names, the date and place of marriage, the ages of both parties and the names of their parents.

These records were supplemented from three sources: the parish records of births and marriages from 1805–1854; the census household enumerations by decade from 1841; and 3-generation pedigrees obtained by interview of elderly persons living on Barra at present. Through the parish and early census reports it was possible to add members to existing sibships and to form new sibships. Children were assigned to a sibship only if identification was unambiguous. If an individual was a parent to more than one sibship, the later sibships were identified by a link to the first sibship. A total of 2575 sibships were identified. Because of missing information and other considerations some of them are excluded from the tabulations for isonymy, migration, and genealogy.

For isonomy, surnames were coded into 26 classes, with the rarer names grouped by origin and similarity. To study kinship between localities in Barra the area was divided into 14 localities of similar size, based on numbers and geographical location (Fig. 2). For migration and kinship with populations outside Barra five areas were chosen (based on the numbers and pattern of migration): namely, South Uist, other Outer Hebrides, Inner Hebrides, Scottish Highlands, and the rest of Scotland (Fig. 1). To derive linear distances among localities and among populations, the coordinates of latitude and longitude were appended to the data.

THE MCNEILS

The McNeils of Barra are the senior branch of the family in Scotland, claiming descent from Tara's Neil of the Nine Hostages. When Gill-Amhanain, the first McNeil of Barra, received his charter from the Lord of the Isles in 1427, the clan system was already entrenched in the Highlands. The names McKinnon and McDonald are together almost as frequent as McNeil. It is conceivable that they were also present in the fifteenth century.

If Barra is imagined as evolving by constant effective immigration rate m per generation from an infinite external population with a low frequency of McNeils, McKinnons, and

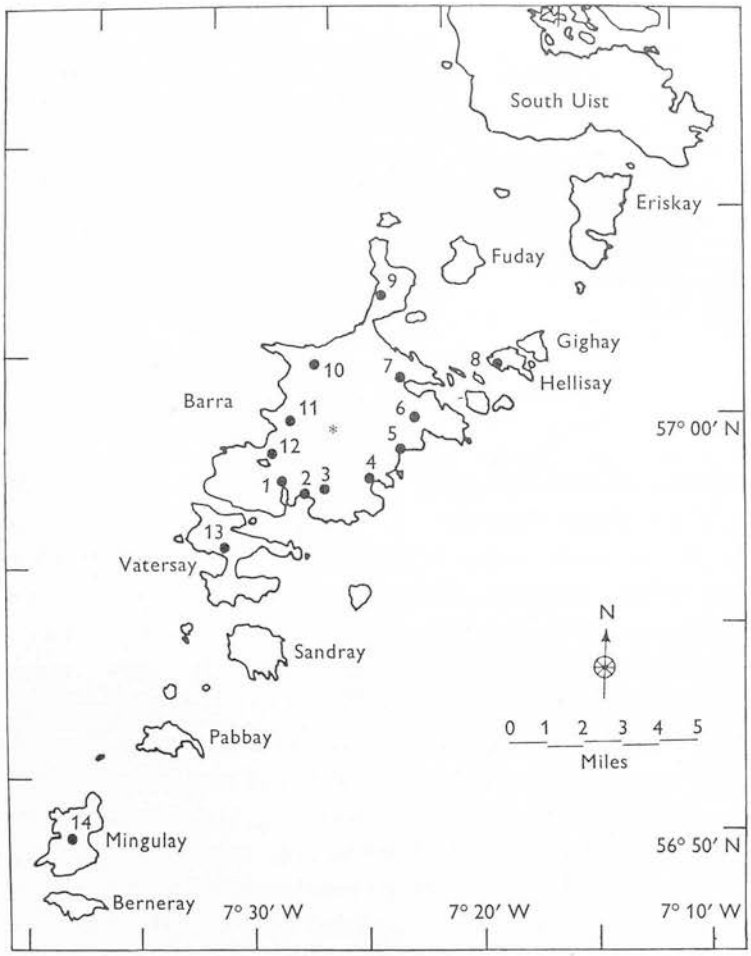

Fig. 2. Map of Barra showing localities chosen for isonymy and migration analysis.

Table 3. *Frequency of common surnames on Barra by generation*

Period of birth of parents	Number of parents	McNeil	McNeil, McKinnon, McDonald
1760–1789	487	0·296	0·480
1790–1819	964	0·323	0·530
1820–1849	868	0·252	0·460
1850–1879	788	0·227	0·485
1880–1909	728	0·247	0·475
1910–1939	335	0·263	0·438

McDonalds, and time in generations of 30 years since 1450 A.D. when Barra may have lacked other surnames is denoted by $t = (Y - 1450)/30$, where Y is year of birth of an individual in the genealogy not known to be born outside Barra, then the frequency P_t of these surnames in year Y, generation t, would be given by

$$P_t = e^{-mt}.$$

For the data in Table 3 the least squares estimate of m would be

$$m = 0{\cdot}0546 \pm 0{\cdot}0023.$$

Evidently, there has been appreciable immigration into Barra during the last five centuries.

ISONYMY

The frequency of individuals with the same surname can be used to estimate kinship within and between groups. This can be applied either to random pairs (random isonymy) or to pairs of mates (marital isonymy). If all individuals with the same surname are supposed to have obtained it from a common ancestor (i.e. are monophyletic), the random kinship ϕ_{ii} for group i relative to a region is given by (equation 12 of Morton *et al.* 1971*b*)

$$\phi_{ii} = (\sum_k q_{ki}^2 - \sum_k Q_k^2)/4(1 - \sum_k Q_k^2),$$

where q_{ki} and Q_k are the frequencies of surname k in group i and in the region, respectively (Crow & Mange, 1965). Unbiased estimators of these quantities are given by equation 25 in Morton *et al.* 1971*b*. For pairs of groups (i, j), separated either in time or space or both, we can derive the kinship ϕ_{ij}, giving a kinship matrix for the population

$$Q_{ij} = (\sum_k q_{ki} q_{kj} - \sum Q_k^2)/4(1 - \sum Q_k^2).$$

Initial estimates of kinship relative to a defined region or time (as given in the tables and figures) are correlations which may have negative expectation (or a positive expectation but be negative through estimation error). When adjusted to an indefinitely large region or time (as in the parameters a and F_{IT} below), kinship is a probability of identity by descent and so has positive expectation (see Crow & Kimura, 1970). The two systems are related by a scalar, here designated as L (Morton, 1973).

Random isonymy: space

Random kinship by distance was estimated for (1) localities within Barra and (2) Barra with other populations. There is first an abrupt fall and then a continued gradual decline in kinship with distance in both sets of data (Table 4). The equation

$$\phi_d = ae^{-bd}(1 - L) + L \qquad (1)$$

was fitted to summarize these results, estimating a, b and L simultaneously, where a is the kinship within a single locality, b is the rate of decrease in kinship with distance and L is the kinship at large distances relative to random gametes from the region. Estimates of these parameters are given in Table 4 along with the fitted values $\hat{\phi}_d$.

Kinship within localities relative to Barra, corresponding to the F_{IS} of Wright (1943), is estimated by $\hat{a}_1 (1 - \hat{L}_1) + \hat{L}_1 \doteq 0{\cdot}0042$, where the suffix 1 refers to the relation between ϕ_d and distance d in kilometres within Barra. This initial value, followed by a sharp fall in kinship even with small distances (1–3 km), indicates some degree of genetic relatedness existing within localities despite their lack of isolation. Random kinship in Barra (Wright's F_{ST}) is estimated by $\hat{a}_2 \doteq 0{\cdot}0042$ (see Table 4). The estimated kinship within Barra localities relative to Scotland would then be (Wright 1943)

$$F_{IT} = F_{ST} + (1 - F_{ST}) F_{IS} \doteq 0{\cdot}0084.$$

Table 4. *Isonymy estimates of kinship by distance*

(1) Localities within Barra

Distance (km)	Weight	Observed $\phi_d \times 10^3$	Expected $\phi_d \times 10^3$
0–1	1207	4·21	4·23
1–2	371	1·13	0·78
2–3	554	−0·36	−0·16
3–5	1262	−0·82	−0·48
5–7	2129	−0·29	−0·55
7–10	917	−0·84	−0·56
10–18	605	−0·81	−0·56
18–30	796	0·16	−0·56
30+	348	−1·23	−0·56

$\hat{a}_1 = 0{\cdot}0048 \pm 0{\cdot}0004$, $\hat{b}_1 = 1{\cdot}242 \pm 0{\cdot}4111$, $\hat{L}_1 = -0{\cdot}0006 \pm 0{\cdot}0002$.

(2) Barra with other regions

Distance (km)	Weight	Observed $\phi_d \times 10^3$	Expected $\phi_d \times 10^3$
0	1207	0·61	0·59
23	153	−2·07	−1·53
55	50	−1·57	−2·84
112	72	−2·27	−3·47
250	256	−3·97	−3·60

$\hat{a}_2 = 0{\cdot}0042 \pm 0{\cdot}0007$, $\hat{b}_2 = 0{\cdot}0311 \pm 0{\cdot}0201$, $\hat{L}_2 = -0{\cdot}0036 \pm 0{\cdot}0007$.

Kinship matrices may be summarized in various ways (Morton & Lalouel, 1973). The program PHEIGEN (Lew, 1973) uses principal component analysis with centroid adjustment, plotting the vectors for the first two eigenvalues. To show the relative importance of the two eigenvalues, the vectors are scaled by the square root of the eigenvalues. To display the points in a geographically convenient form, a program MATFIT (Lalouel, 1973) was used to obtain maximum congruence with the X and Y geographical co-ordinates. A measure of fit of the first two eigenvalues is given by the product-moment correlation (R_1) between genetic distance defined as $\phi_{ii}+\phi_{jj}-2\phi_{ij}$ (Morton *et al.* 1971*b*) and its two-dimensional approximation by the first two eigenvectors. Similarly a correlation (R_2) gives an estimate of the fit of the eigenvectors to the geographical co-ordinates.

The plots of the first two vectors of the principal component analysis of the kinship matrix are given in Fig. 3. Both within Barra and among populations the first two eigenvalues give a good fit to the kinship matrices ($R_1 = 0{\cdot}92$, $0{\cdot}96$). The two diagrams also reproduce to a considerable extent the geographical co-ordinates ($R_2 = 0{\cdot}32$, $0{\cdot}80$). This shows that kinship estimated from isonymy depends largely on isolation by distance. In contrast, tree diagrams (dendrograms) constructed from the kinship matrices gave ambiguous results and do not seem to be a reliable method of displaying kinship among poorly differentiated populations.

Random isonymy: time

Kinship among generations can also be studied by random isonymy. Using equation (1), but replacing d for distance by t = time in generations gave estimates $\hat{a} = 0{\cdot}0023 \pm 0{\cdot}0011$, $\hat{b} = 0{\cdot}1955 \pm 0{\cdot}1316$ and $\hat{L} = -0{\cdot}0018 \pm 0{\cdot}0011$. Kinship in one generation relative to the whole

period is then $0{\cdot}0005 \pm 0{\cdot}0016$, from $\hat{a}(1-\hat{L})+\hat{L}$. This measures the amount of kinship incurred per generation on Barra.

The principal component analysis of the generation kinship matrix by its first two vectors allocated different generations to different quadrants, with almost the correct ranking of generations and similar distances between the generations. Again the dendrogram drawn from the kinship matrix could not be interpreted on the basis of lineal descent.

Marital isonymy

The mean inbreeding coefficient in Barra relative to contemporary panmixia was estimated from marital isonymy by

$$\alpha = (I-\Sigma q_i^2)/4(1-\Sigma q_i^2),$$

where I is the frequency of isonymous marriages and q_i is the frequency of surname i. This analysis was restricted to parents of living and/or fertile sibships, thus excluding temporary immigrants. Some 10 % of the marriages were isonymous, and the mean inbreeding coefficient was estimated as 0·0007. Thus internal deviations from panmixia are negligible relative to accumulated genetic drift of the whole isolate.

MIGRATION

The rates of migration within Barra and immigration into Barra can also give useful information on kinship and on population structure. These rates can be simply measured by comparing the birth places of parents and their offspring. The distributions of places of birth of fathers and of mothers for *fertile* individuals born on Barra are given in Table 5. Temporary migrants are thus excluded since their offspring must also have children born on Barra to qualify as fertile individuals.

About one third of those with Barra parents were born in the same locality of Barra as their parents. This indicates a considerable degree of stability in family residence over time, especially since the local populations were small (about 40 persons per generation per locality) and the distances between localities are also small (2–20 km).

The overall rate of immigration to Barra was 8·6 % and was similar for males and females. Of this 6·1 % came from the Inner and Outer Hebrides, 0·8 % from the Scottish Highlands and 1·7 % is the 'long-range' migration rate from the rest of Scotland. The ratios of male to female migrants from the different sources were variable, and unlike previous studies (Morton *et al.* 1971*a*), long-range migrants were not predominantly male.

To relate migration rates to kinship and population structure the effective size of the various populations and the migration *inter se* are required. The figures for the 1971 population census are given in Table 5, along with the estimated mean population size over the past 150 years. Barra, like most of the Highlands and Isles, has suffered large losses in population over this period.

The sources and numbers of immigrants to Barra are affected by the dominance of Roman Catholicism on the island. This must be an important isolating factor for Barra in mainly Protestant Scotland, and largely limits the choice of immigrants to those from other Catholic communities in the Hebrides and Highlands. South Uist is also largely a Catholic island, but the proportion of Catholics in the other Hebrides and in the Highlands is only about 5 %

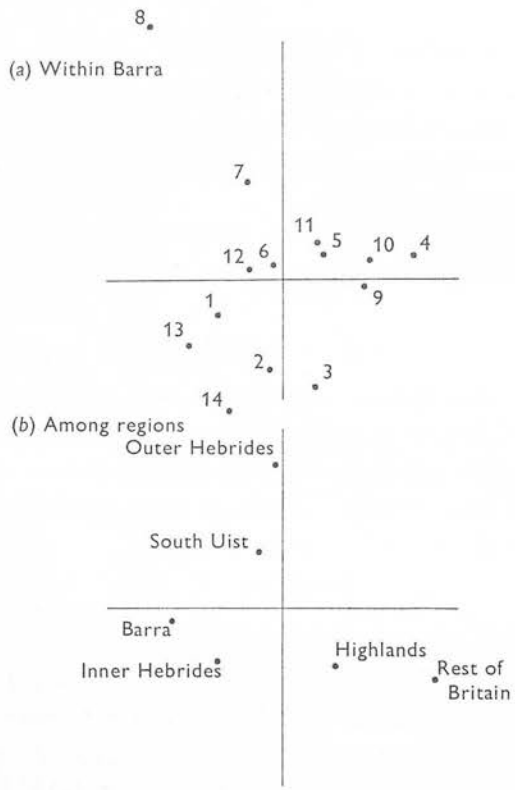

Fig. 3. Plot of the first two eigenvectors of the isonymy matrix of kinship (*a*) within Barra (cf. Fig. 2) and (*b*) among areas (cf. Fig. 1).

Table 5. *Immigration into Barra and estimated effective population size (Roman Catholic) for* 1820–1970

Population of birth of parent	Number of parents of fertile individuals born on Barra		Mean distance from Barra (km)	Population		Population Roman Catholic	Estimated effective R.C. mean population (1820–1970)
	Fathers	Mothers		1971 census	Estimated mean (1820–1970)		
Same Barra locality	675	625	—	—	—	—	—
Any Barra locality	1793	1794	—	1080	1500	0·94	470
S. Uist and Eriskay	40	85	25	3870	5000	0·70	1167
Other Outer Hebrides	46	28	86	25,600	32,000	0·05	530
Inner Hebrides	26	14	60	10,000	24,000	0·05	400
Scottish Highlands	6	24	127	231,000	400,000	0·05	6670
Other parts of Scotland	36	29	265	5,000,000	4,500,000	0·15	675,000
Total	1947	1974					

Catholic Directory, 1973). For the rest of Scotland, the rate is about 15 %. Taking the effective population size as one-third of the mean population size over 150 years, and allowing for the proportion of Catholics, gives estimates of the mean Catholic effective size for each region (Table 5).

The migration matrix of absolute numbers of migrant individuals among localities within Barra is given in Table 6. The numbers migrating between two localities have been averaged to obtain symmetry and so prevent the array of population sizes changing through apparent differential migration rates. The estimated effective population size for Barra was 470 and the effective number for each locality was taken in proportion to the number of parents recorded in the locality, multiplied by the ratio of the evolutionary to the effective size (690/470) estimated below. The migration matrix among regions (Table 6) was derived from the frequency of migrants into Barra multiplied by the smaller population size for the pair of regions studied. The diagonals were obtained by multiplying the estimated effective size (Table 5) by the factor (7·6 = 3587/470) found for Barra.

Effective migration rate

Without knowing effective population sizes, an estimate of the effective migration rate (m_e) into Barra can be got from Malécot's (1948) approximation

$$m_e = \sqrt{[m(m+2k)]},$$

where m is the long-range migration rate and k is the short-range migration rate after long-range migrants have been excluded. For Barra $m = 0{\cdot}0166$ and $k = 0{\cdot}0698$, giving an estimate of $m_e = 0{\cdot}0509$ for the effective migration rate into Barra. This is closely comparable to the estimate of 0·0546 from isonymy during the last five centuries.

Evolutionary size and migration

From the data on migration rates and on effective population sizes of the regions, estimates of the evolutionary population sizes and effective migration rates can be derived (Morton, 1973). Taking the long-range migration pressure as $m = 0{\cdot}0166$ (ignoring mutation and selection), the identity

$$\phi_{ij}^{(t)} = (1-m)^2\{\sum_k \sum_h p_{ki}\, p_{hj}\, \phi_{kh}^{(t-1)} + \sum_k p_{ki}\, p_{kj}\, (1-\phi_{kk})/2N_k\} \qquad (2)$$

gives the kinship between regions at generation t, where N_i are the estimated effective population sizes and p_{ij} are the migration rates between regions (Table 6*b*). The results for successive generations were obtained by the program OBELIX (Harris, 1973). Stability of the kinship matrix was reached after 122 generations (although approached in a much smaller number), with the equilibrium values for kinship and inbreeding in Barra relative to the rest of Britain being 0·0077 and 0·0070 respectively. With due caution about the propriety of assuming constant values of N and m over many generations, the estimates are at least consistent with other evidence. A two-dimensional representation of the localities according to their components along the first two eigenvectors of the equilibrium kinship matrix (Fig. 4) shows that migration mirrors the geography of the area ($R_1 = 0{\cdot}94$, $R_2 = 0{\cdot}60$). This topology does not depend critically on the equilibrium assumption, since it is approached in a few generations.

Table 6. *Migration within and into Barra*

(*a*) Within Barra

Locality of birth	Locality of parents' birth													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1	156	16	17	7	2	2	2	1	2	3	14	31	17	11
2	.	35	50	11	6	3	6	0	2	1	5	6	8	13
3	.	.	140	15	12	1	7	1	8	7	15	4	10	12
4	.	.	.	175	60	4	26	1	3	19	20	1	2	3
5	.	.	.	.	127	18	12	5	3	16	10	1	0	3
6	.	.	.	.	.	32	37	5	9	5	5	0	0	2
7	.	.	.	.	.	.	129	23	13	3	18	4	1	0
8	.	.	.	.	.	.	.	12	3	7	3	3	0	0
9	.	.	.	.	.	.	.	.	8	6	9	1	0	1
10	.	.	.	.	.	.	.	.	.	32	31	5	0	0
11	.	.	.	.	.	.	.	.	.	.	211	18	1	7
12	.	.	.	.	.	.	.	.	.	.	.	116	5	14
13	.	.	.	.	.	.	.	.	.	.	.	.	13	22
14	.	.	.	.	.	.	.	.	.	.	.	.	.	114
Effective size	59	35	59	81	58	33	68	15	22	47	98	47	23	50

(*b*) Barra with other regions (symmetrized matrix)

Place of birth	Place of parent's birth				
	Barra	South Uist	Outer Hebrides	Inner Hebrides	Highlands
Barra	3587	125	74	40	30
South Uist	(125)	(8869)	(149)	(50)	(67)
Outer Hebrides	(74)	(149)	(4028)	(50)	(50)
Inner Hebrides	(40)	(50)	(50)	(3040)	(46)
Highlands	(30)	(67)	(50)	(46)	(50700)
Effective size	(470)	1167	530	400	6670

(Bracketed values are estimates; see text.)

The equilibrium value and the rate of approach to equilibrium allow estimation for each region of the evolutionary population size (which exceeds the effective size because of migration) and of the effective migration rate using the relationship (Morton *et al.* 1973)

$$\Phi^{(t)} = \left(\frac{1}{4N_e\, m_e + 1}\right) 1 - e^{-(2m_e + 1/2N_e)t}. \tag{3}$$

Since m_e and N_e are estimated from $\phi^{(t)}$, rather than directly from such demographic variables as fertility, they include the effects of migration and population growth.

The solution for $\phi^{(t)}$ for Barra was obtained by the program DEMOGEN (Yee, 1973), with simultaneous estimation of N_e and m_e. The evolutionary size was estimated as 690 ± 40 and the effective migration rate as $0{\cdot}0482 \pm 0{\cdot}0030$. The latter is in good agreement with 0·0546 from common surnames and 0·0509 from Malécot's approximation.

These estimates of evolutionary size and migration can be used, with Table 6*a*, to predict the equilibrium kinship and inbreeding values within Barra, using equation (2) as before. The

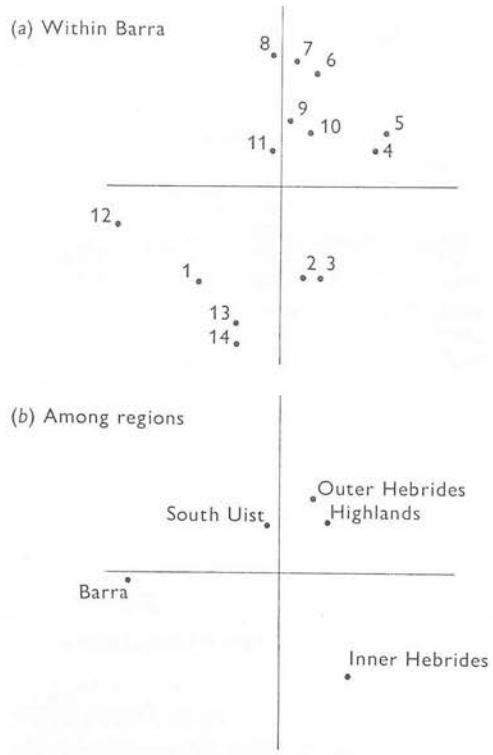

Fig. 4. Plot of the first two eigenvectors of the equilibrium migration matrix of kinship (*a*) within Barra (cf. Fig. 2) and (*b*) among regions (cf. Fig. 1).

mean kinship for the Barra localities at equilibrium (66 generations) relative to the rest of Britain were found to be 0·0092, which is close to the value of 0·0084 from random isonymy. The random kinship within Barra was 0·0070. The two-dimensional display of the first and second vectors of the equilibrium kinship matrix ($R_1 = 0{\cdot}91$) gives a realistic fit to the geographical array of the 14 localities ($R_2 = 0{\cdot}57$), showing that migration declines with distance. As with isonymy, localities 9, 10 and 11 are grouped close to localities 4, 5 and 6, with which they are connected by an old path across the island. This suggests that travel between these areas was more often overland than around the coastal road as at present.

Genealogy

For analysis of genealogy only current sibships and parents of fertile sibships were included, thus eliminating temporary migrants and infertile sibships. This left only 1194 sibships out of the original 2575 collected. The program COEF (Lew, 1973) calculates inbreeding for each sibship, tracing all paths through the parental sibship numbers and allowing for half-sibships through a link to the common parental sibship. If a parental sibship number is not given, a unique number is assigned, up to a limit of 2000 total sibships. Some 415 paternal and 392 maternal sibship numbers were not known, and 312 sibships had neither parental sibship number recorded.

Only 16 of the 1194 sibships were found to have common ancestors in the genealogy collected. There were no close consanguineous matings recorded, the closest relationship between mates being that of second cousins ($F = 0{\cdot}0156$). The mean inbreeding coefficient was 0·010 for the

Table 7. *Chain lengths and accumulated random kinship on Barra*

Chain length	Number of chains	Observed accumulated kinship $\times 10^3$	Estimated accumulated kinship $\times 10^3$ (Fitted curve)	Corresponding generation number
3	69	0·86	0·75	1·0
4	81	1·37	1·10	1·5
5	92	1·66	1·43	2·0
6	111	1·83	1·74	2·5
7	201	1·99	2·04	3·0
8	557	2·21	2·33	3·5
9	1091	2·42	2·60	4·0
10	1517			
11	1028			
12	188			
13	12			

N_e (given $m_e = 0{\cdot}048$) $= 638 \pm 24$.
Equilibrium random kinship $1/(4N_e\, m_e + 1) = 0{\cdot}0081 \pm 0{\cdot}0003$.

16 consanguineous sibships and 0·00013 for all sibships. This indicates a considerable avoidance of consanguineous matings within the degree for which dispensation is made by the Roman Catholic church.

To estimate random kinship among individuals in Barra, random pairs of sibships were generated by the program FRIEDMIX (Harris, 1973). These were restricted to sibships born in the last two generations, permitting sib mating but not self-fertilization. A total of 9999 pairs were generated. The program KIN (Lew, 1973) calculates the coefficient of kinship among these random pairs and gives the distribution of lengths of chains of relationship (Table 7).

If n_i is the number of chains of length i for N pairs, then the contribution to inbreeding or kinship is $n_i\, 2^{-i}/N$. In generation $t = (i-1)/2$ the cumulative value is $\phi_t = \sum_{i=1}^{t} n_i\, 2^{-i}/N$. Beyond chains of length 9, the numbers of chains fail to double per additional link and then fall off rapidly due to the limited span of the genealogies collected. The cumulated random kinship from genealogy reaches 0·0024 after 4 generations (Table 7). (N.B. There are two links in the chain, one backward and one forward, for each generation.) Fitting equation (3) with $m_e = 0{\cdot}048$ to the trend up to chains of length 10 and putting $t = \infty$ gives an equilibrium random kinship of $0{\cdot}0081 \pm 0{\cdot}0003$ and an evolutionary population size of 638 ± 24.

DISCUSSION

To put Barra into perspective we need to know something about genetic variation in Britain. A recent symposium on this topic did not mention kinship, and references to the inbreeding coefficient were restricted to a paper by Rawlings (1973) which baldly stated that 'to date there has been no investigation of inbreeding in England.' This is a slight exaggeration. In a remarkable paper G. H. Darwin (1875) developed the concept of isonymy and applied it to estimating the frequency of cousin marriage. Mendel's work lay fallow for another generation, and nearly a century passed before Crow & Mange (1965) refined what Darwin had formulated inductively. In the interval only Arner (1908) used Darwin's results, which indicated an inbreeding coefficient of 0·0029 in nineteenth-century England and of 0·0037 for Burke's landed gentry

(Yasuda & Morton, 1967). Later Julia Bell (1940) reported that the inbreeding coefficient had declined to 0·0004 in the general hospital population of England and Wales.

Isonymy in the Northumberland parish of Warkworth indicates that inbreeding went from 0·0018 at the end of the seventeenth-century to 0·0072 at the beginning of the nineteenth. Other European isolates behaved similarly during this period of population growth, with subsequent decline of inbreeding as population mobility increased. A useful summary was given by Freire-Maia (1957). Barra appears typical of European isolates a century ago and comparable to Alpine villages at the present time (Morton, 1974).

Inbreeding coefficients in excess of 0·01 occur for a few European religious isolates, but are common for slash-and-burn agriculturalists and atoll dwellers (Morton, 1974). It is tempting to speculate that pre-agricultural Europe was characterized by similarly high differentiation, the residue of which was apparent among tribes in Roman times. Drift among these groups may well account for regional concentrations of rare genes, such as cystic fibrosis in north-western Europe and phenylketonuria in Ireland. More restricted distributions reflect drift since Roman times, as Tay-Sachs disease and pentosuria in Eastern European Jews and epidermolysis bullosa in Norway. The low inbreeding rate on Barra is not likely to produce any startling gene frequency change. Indeed, the only detected rare gene of interest is for the Ellis Van Crevald syndrome, which occurs in two sibships related as first and second cousins. However, neither pair of parents has a known common ancestor. The founder for this gene probably occurred as a mutant or migrant in the eighteenth century or before, and the long waiting time to homozygosis is to be expected in a population with as large an evolutionary size as Barra.

Among all the methods to study population structure, prediction of kinship and inbreeding from migration and genealogy is unique in permitting a quantitative comparison with estimates from isonymy and bioassay of genetic systems. We have seen that isonymy agrees with prediction. For a genetic polymorphism with homozygosity ΣQ^2 in Britain, the expected homozygosity on Barra is $\Sigma Q^2 + 0{\cdot}007\ (1 - \Sigma Q^2)$. The increase is negligible from most epidemiological points of view but is sufficient to permit bioassay of kinship (Morton *et al.* 1971). It will be interesting to compare gene frequencies on Barra with this prediction.

SUMMARY

Historical demography, surname concordance (isonymy), migration, and genealogy give a consistent description of population structure. The census size has averaged about 1400 over the last five centuries. Conjoined with an effective migration rate of 0·05 per generation as estimated by three different methods, this gives an evolutionary size of 638, random kinship of 0·008 and inbreeding of 0·007 relative to the rest of Britain. The population structure of Barra is similar to other British isolates in the recent past, but an order of magnitude less inbred than slash-and-burn agriculturalists and Pacific Islanders. Some consequences for rare genes and polymorphisms are discussed.

We are indebted to Mrs Frances Hill, Mrs E. Baxendine, Mrs S. Collyer, Mrs R. Demey, Mrs K. Ewart and Mrs B. Wilson for their diligence and care in abstracting the material and reconstructing families and pedigrees.

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Copies of the data file used for this analysis may be obtained from NAPS, no. .

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THE IMPORTANCE OF DETERMINING THE MODE OF INHERITANCE FOR THE ESTIMATION OF RECURRENCE RISKS

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THE IMPORTANCE OF DETERMINING THE MODE OF INHERITANCE FOR THE ESTIMATION OF RECURRENCE RISKS

*by Nicole VAN REGEMORTER * and Charles SMITH ***

In simple Mendelian disorders the mode of inheritance is known and recurrence risks can be derived from genetic theory, even for complex family histories (Heuch and Li, 1972). But for many familial disorders the mode of inheritance has not been established and discrimination between different models has proved very difficult because various models can fit the observed data (James, 1971; Smith, 1971a; Krüger, 1973; Kidd and Cavalli-Sforza, 1973). In genetic counselling for such disorders so-called empiric risks are used. These are based on observation rather than on any genetic theory. They measure average risk for all families rather than applying to a particular counselling case and do not take into account other factors affecting the risks such as the family history or severity. By contrast, if the genetic model is specified, recurrence risks can be derived specifically for each counselling case. The object of this paper is to compare recurrence risks derived by two extreme genetic models to assess how important the model is in affecting the recurrence risks obtained.

Models

The two extreme models of inheritance of familial disease are the single locus and the multifactorial models. Many intermediate models could also be considered and it is implied, but not proven, that the range of risks for the extreme models should also cover the risks estimated from intermediate models.

The generalised single locus 2-allele model can be written (Elston and Campbell, 1970; Morton, Yee and Lew, 1971) as :

Genotype	AA	Aa	aa
Frequency	p^2	$2pq$	q^2
Proportion affected	f_{AA}	f_{Aa}	f_{aa}

An equivalent form has been used by Reich, James and Morris (1972) and by Kidd and Cavalli-Sforza (1973), with individuals of the same genotype being normally distributed about their mean, μ_{AA}, μ_{Aa}, or μ_{aa}, with a common variance (σ^2) and with proportions f_{AA}, f_{Aa} and f_{aa} respectively being above a given threshold value on the distribution scale and so being affected. James (1971) showed that, in terms of familial frequencies, the model has only three independent parameters, the gene frequency (q) and the additive (V_A) and dominance (V_D) genetic variances. Thus different parameter sets for q, f_{AA}, f_{Aa} and f_{aa} may give the same set of familial frequencies.

The multifactorial model used is the liability model of Falconer (1965) with a continuous underlying normal distribution and single threshold. From familial frequencies, the correlation in liability between relatives can be estimated and if common familial environmental effects can be discounted, the heritability of liability can be derived.

Overlap of models

The interest is in situations where both models provide an adequate statistical fit to observed data on familial frequencies, or on segregation data for families. If the fit to the data by a model is not adequate then that model can be rejected and need not be considered in risk estimation. The first step then is to find the range parameter sets of the two models for which overlap occurs.

With the multifactorial model the heritability must be less than 100% and should be similar for different degrees of relationship (unless there are important dominance and epistatic effects which give higher estimates for monozygous twins and full-sibs) (Falconer, 1960). Thus significant differences between heritability estimates from different relatives, or estimates significantly exceeding 100% will indicate that the multifactorial model is inappropriate. In practice, however, it will be important to discount common familial environmental effects which will also lead high heritability estimates.

James (1971) showed that the single locus model will be able to fit multifactorial data, except when there is significant epistasis. This could arise from classifying the underlying continuous liability into 0, 1 (normal, affected) classes when the disease frequency is low and the heritability is high (Dempster and Lerner, 1950). The areas of fit of the multifactorial model to single locus model data are examined here empirically and are illustrated in Figure 1. Consider two population frequencies (F), 1% and 0.1%. To restrict the choice of parameter sets let $f_{aa} \geq f_{Aa} \geq f_{AA} \geq 0$; that is *a* is a deleterious gene but there may be a proportion f_{AA} of sporadic cases among AA individuals. Almost any form of gene action, apart

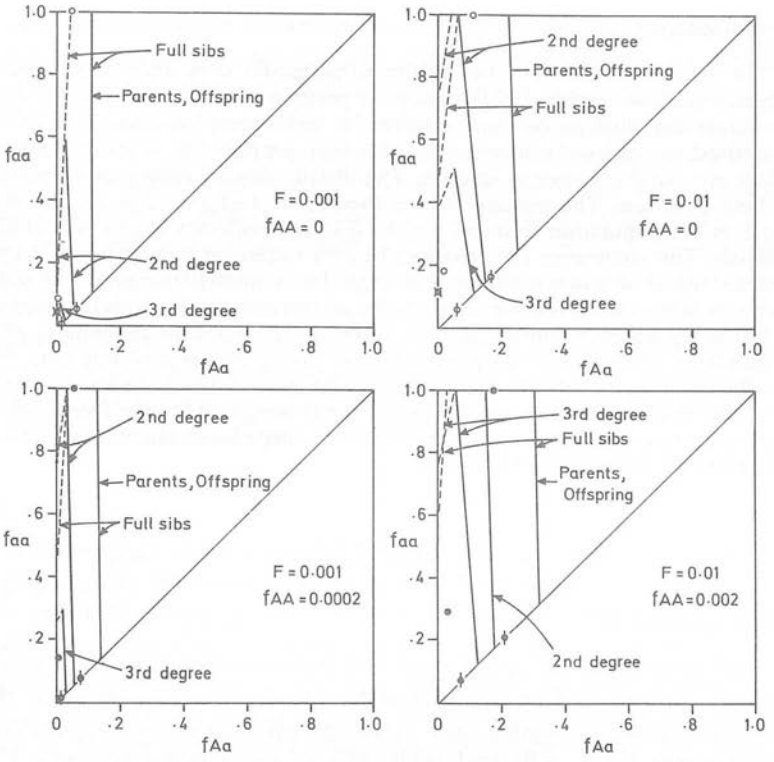

Figure 1 : Areas of overlap (with heritability values less than 100%) for different kinds of relatives and different parameter sets. Areas of overlap are to the left of the solid line and to the right of the broken line (where present) for different relatives.

(left, right – population frequencies 0.1%, 1%
upper, lower – no sporadic cases, 20% of cases sporadic).

The sets of parameters selected for evaluation of risks are shown on each graph, corresponding to heritability values of 40% (left) and 80% (right) [see Table I, for values; Figure 2 for symbols].

from heterozygote advantage, is covered despite the restriction. From these parameters (F and f's) the gene frequency can be calculated and the frequencies in various kinds of relatives of affected probands can be derived using the expressions given by James (1971). These can then be used to calculate heritability estimates for different sets of relatives namely, monozygous (MZ) twins, parents and offspring, full sibs, 2nd degree relatives and 3rd degree relatives. Many of the sets of parameters give heritabilities greater than 100%. By trial and error boundaries on the parameter sets can be found giving heritabilities equal to or less than 100% for different kinds of relatives. Similarly sets of f parameters could be found corresponding to different heritability values, as if these were estimated from the same set of observed data, and these provided the parameter sets for comparing the recurrence risks with the two models.

Risk estimation

The recurrence risks for the multifactorial model were derived by a numerical integration method (Smith, 1971b) using the program RISKMF (Smith, 1972). These are accurate for sibships but approximate for more complex family histories. Another method to estimate recurrence risks has been proposed by Morton (1969) where the risks are variable between sibships. The distribution of risks may be represented by a beta function. The parameters are then $A = (1-F_R) / (F_R-F)$ and $B = AF$, where F is the population frequency and F_R is the frequency in relatives of affected individuals. The recurrence risk, given s sibs with r affected is then $(B+r) / (A+s)$. To determine the recurrence risks for the single locus model, the gene and genotype frequencies were calculated for each set of penetrance rates for both disease frequencies. For every possible combination of parental genotypes the probability of having the considered sibships and the probability of having the same sibship with the next child affected were calculated. The recurrence risks was taken to be the inverse of the *ratio* of the sums of the two sets of probabilities weighted by the frequency of the parental genotypes. A check on the risks for the single locus model was made by the program PEDIG (Heuch and Li, 1972).

RESULTS

Overlap of models

The extent of the overlap of the parameters of the two models is shown in Figure 1. The left and right graphs refer to different disease frequencies and the upper and lower graphs represent respectively no sporadic cases ($f_{AA} = 0$) and with 20% of cases being sporadic ($f_{AA} = 0.2F$). With $f_{aa} \geq f_{Aa}$, no points can fall below the diagonal lines. Acceptable values of heritability (that is, less than 100%) are obtained with parameter sets to the left of the solid lines and to the right of the broken lines (where present) for different types of relatives.

The MZ heritabilities, of course, cannot exceed 100%. The full-sib heritabilities are similar to the parent and offspring values except when the situation tends towards a strict recessive form of inheritance, that is if f_{Aa} is low and f_{aa} is high. A general result was that the heritabilities for 3rd degree relatives are larger than for 2nd degree which in turn are larger than for parents and offspring. Thus the boundaries for acceptable heritability values become more restrictive as the degree of relationship decreases, as shown in Figure 1. With low disease frequencies the area of overlap of the two models is very small, but it increases as the proportion of sporadic cases increases and as the disease frequency increases. Note that it should usually be possible to distinguish dominant inheritance with incomplete penetrance from multifactorial inheritance because there is little overlap of the models, except when f_{Aa} is low (that is penetrance is very low).

A more restrictive criterion for overlap of the two models would be to find parameter sets which give heritabilities which are similar for different kinds of relatives. With multifactorial inheritance the expected heritabilities are the same for all relatives if there is no dominance or epistasis, and are always the same for parents, offspring, 2nd degree and 3rd degree relatives. As already noted with the single locus model, the heritability values usually increased as the degree of relationship fell, and it was often difficult to find parameter sets which gave equal heritabilities for all classes of relatives. The heritability values change in a regular manner as they deviate from the boundary lines in Figure 1, but not at the same rate over different sections of the graphs. It would be possible to draw contour lines of heritability values to indicate the shape of the response surface and in this way find if there are areas which give similar heritabilities for the different kinds of relatives.

Risks

To compare the recurrence risks estimated from the two models, two population frequencies (1% and 0.1%) and two levels of heritability (80% and 40%) were chosen. Several parameter sets for the single locus model satisfying these situations were selected to cover a range of possible values and these are given in Table I. Their positions in the overlap areas are shown in Figure 1 and the symbols used are given in Figure 2. These parameter sets were chosen to satisfy the parent-offspring heritabilities, since these are most reliably estimated in practice, but they may give much higher heritability estimates for 2nd and 3rd degree relatives as is obvious for Figure 1. The range of up to 20% sporadic cases allows for substantial noise due to phenocopies, mutations and other non-recurrent factors. Thus the series of parameter sets chosen should cover a wide range of likely sets obtained in analysis of data on frequencies or segregation in families of affected individuals.

The recurrence risks can then be evaluated for a series of sibships, or more complex family histories, with the different models and parameter sets. The results for sibships with 0, 1 and 2 affected parents are presented in Figure 2 for different population frequencies and heritabilities. Two general results are shown by these graphs. First, there may be large differences in risks predicted from different parameter sets for the single locus model, especially for sibships with two or more affected individuals (including parents). Second, there will usually be one or more parameter sets which will give risks similar to those predicted by the multifactorial model. This tends to occur when the penetrance rate in homozygotes (f_{aa}) takes the largest value possible for the particular set of circumstances, that is for the frequency, heritability and proportion

TABLE I :

The sets of parameters for the single locus model chosen for study to represent the area of overlap with the multifactorial model (see Figure 1). The gene frequencies and the heritability estimates derived from the expected incidences in relatives are also given

Population frequency	Heritability (%)	Single locus parameters f_{AA}	f_{Aa}	f_{aa}	Gene frequency	Derived Heritability (%) MZ twins	Parent-Offspring	Sibs	2nd degree	3rd degree
0.010	80	0.000	0.165	0.165	0.031	56	80	80	108	137
		0.000	0.110	1.000	0.040	68	80	91	108	137
		0.002	0.205	0.205	0.020	57	80	81	109	138
		0.002	0.175	1.000	0.022	59	80	83	108	137
0.010	40	0.000	0.060	0.060	0.087	32	40	41	49	56
		0.000	0.020	0.180	0.160	42	40	49	49	57
		0.000	0.000	0.115	0.295	47	40	54	49	56
		0.002	0.071	0.071	0.060	31	40	40	48	55
		0.002	0.030	0.290	0.101	44	40	51	49	55
0.001	80	0.000	0.059	0.059	0.008	51	80	81	122	177
		0.000	0.043	1.000	0.010	68	80	99	122	177
		0.002	0.073	0.073	0.005	51	80	80	122	177
		0.002	0.064	1.000	0.006	58	80	87	121	176
0.001	40	0.000	0.013	0.013	0.039	28	40	40	54	69
		0.000	0.005	0.080	0.068	42	40	54	55	70
		0.000	0.000	0.078	0.144	48	40	61	54	69
		0.002	0.016	0.016	0.026	28	40	40	54	69
		0.002	0.005	0.140	0.050	49	40	63	55	70

of sporadics concerned. On the other hand with low penetrance rates, the risks quickly reach a plateau and do not increase further with more affected relatives. This is because the risks are limited by the level of penetrance (f_{aa}) in homozygotes, which is also the level of the plateau. By varying the penetrance level virtually any set of risks, within these two extreme sets, could be obtained by the single locus model.

The patterns of the risks in Figure 2 for different frequencies and heritability values are very similar, despite the fact that the parameter sets selected were not the same, being chosen from Figure 1 to represent the range of parameter sets for each situation within a given area of Figure 1. This shows that the patterns are conservative and will represent a variety of parameter sets. The risks with no sporadics ($f_{AA} = 0$) are usually somewhat higher than with sporadics, but the differences were not large. With high penetrance values the risks increased to very high levels with increasing family history. This is because with more sibs or parents being affected, the probability of the next child being homozygous also increases and the risks can rise up to the level of penetrance.

The statistics necessary to calculate the recurrence risks by Morton's model are the incidence in the offspring og matings with 0, 1 and 2 affected parents and the recurrence risk (for each type of family) among sibs of probands. These statistics were then applied separately to Morton's formula to derive the risks. For clarity in Figure 2, the results are given only in the first set of graphs. In general, as before, there can be large differences in the risks estimated by the different methods and the differences are usually larger as the number of affected relatives increases. When the difference between the statistics derived for the two models is large, as in the case for both parents affected, Morton's model tends to give recurrence risks similar to those obtained by the model used to calculate the statistics, as would be expected. When neither parent is affected, the risks are usually intermediate between those obtained by the other two models. This is due to overlap of the statistics derived from the other two models. For the single locus model with very low penetrance rates and with sporadics, the recurrence risks by Morton's model with 1 affected parent and more than 2 affected sibs, are lower than for the same sibship with no affected parent (Figure 2). This is because the two cases use different sets of statistics depending on the parental status, and so direct comparison of the recurrence risks is not possible, in this case.

Comparisons of recurrence risks with more complex pedigrees were also attempted using the multifactorial and single locus models. In general the patterns of the risks with second and third degree relatives

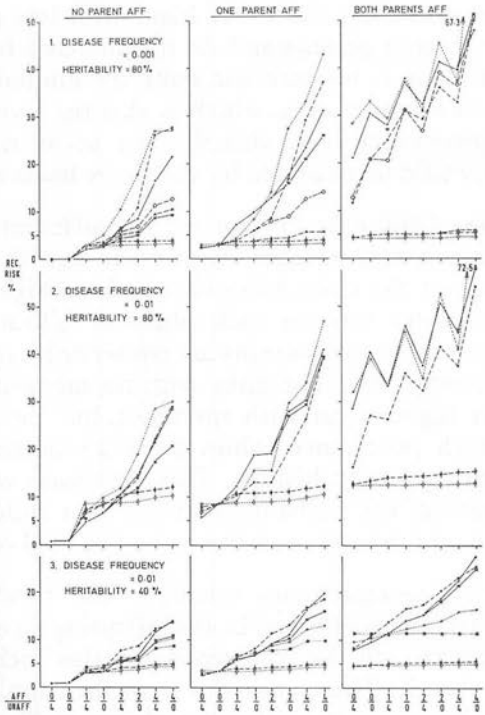

Figure 2: Recurrence risks for various sibships with 0, 1 or 2 affected parents by using different genetic models and different selected parameter sets (see Figure 1 and Table I).

Symbols

Multifactorial model

Single locus model

(1) $f_{AA} = 0$, f_{aa} high — no sporadics, high penetrance

(2) $f_{AA} = 0$, f_{aa} low — no sporadics, low penetrance

(3) $f_{AA} = 0$, $f_{Aa} = 0$, f_{aa} low — no sporadics, low penetrance, no heterozygotes manifesting

(4) $f_{AA} \neq 0$, f_{aa} high — 20% sporadics, high penetrance

(5) $f_{AA} \neq 0$, f_{aa} low — 20% sporadics, low penetrance

Morton's Beta Function Model

Based on multifactorial statistics

Based on single locus case 4

Based on single locus case 5

included were quite similar to those obtained for sibships in that a wide range of possible risks was possible and that the risks diverged with increasing family history.

DISCUSSION

The wide range of recurrence risks possible from different models and sets of parameters shows that the estimation of risks for genetic counselling is likely to be arbitrary and imprecise until the mode of inheritance is known. The methods here may be useful to show the clinician the range in which the risks may fall, but the range is too wide to be useful. Perhaps with collection of further data especially on families with several affected members and perhaps also on 2nd and 3rd degree relatives, the choice among genetic models and parameter sets may be more restricted and the range in estimated risks would be reduced. For example, Woolf (1971) has calculated empiric risks for cleft-lip $\pm$ cleft-palate with two or more relatives of different kinds affected. These tend to be consistently higher than those predicted by the multifactorial model. This result is similar to these in Figure 2 for a gene with high penetrance in homozygotes (aa) but with a proportion of heterozygotes manifesting. However, with these parameters, for high parent offspring heritabilities still higher heritabilities in 2nd and 3rd degree relatives would be expected (see Table I).

In theory discrimination between the different models should be possible because the trends in heritability differ for the two models. Heritabilities exceeding 100% or increasing with decreasing degrees of relationship would indicate a single locus model while uniform heritabilities less that 100% might suggest a multifactorial model. However, in practice it would require a very large amount of good data to allow a reliable discrimination between the models (Smith, 1971a). In fact data on 2nd and 3rd degree relatives are usually much less reliable than on 1st degree relatives and there may be common familial environmental effects which differ between relatives and these will be difficult to avoid or discount.

The single locus model considered here is rather extreme and may be biologically rather unlikely in that it does not allow for any modifying genes (or environmental effects) common to family members. Yet penetrance levels are modifiable by selection. Thus some of the variation in liability about the mean for the genotype will be inherited and affect the risks among relatives. Morton and MacLean (1974) have elaborated a 'combined' model which includes a major locus and background polygenic inheritance. Their approach has been to test for a major locus against

a polygenic background. Results so far (MacLean, Morton and Lew, 1975) show some success in discrimination with continuous traits but with discrete data on disease status the methods of analysis are very much less powerful, so the problems of discrimination may remain.

It is usually possible to find a set of parameters for the single locus model which give an adequate fit to multifactorial data, but not vice versa. The prior probabilities of getting parameter sets in the overlap area are very different for the two models, being low for the single locus model and higher for the multifactorial model. These prior probabilities should be considered in assessing the relative likelihoods of the two models. Thus in data analysis, finding that both models fit the data may point to multifactorial inheritance. For example the parameter sets derived by Kidd and Cavalli-Sforza (1974) to fit familial data on schizophrenia all fit into a very restricted corner of the parameter space. This suggests that their iterative methods have been able to find initially very unlikely sets of parameters to fit multifactorial data. Moreover the dilemma they raise about the apparent difference in a conclusion about importance of genetic factors depending on the model used, is largely due to the way they express their results. Thus the low genetic variance (10-20%) attributed to single locus model is due to the low estimated frequency of their extreme genotypes (Edwards, 1965) and not to the absence of proposed genetic effects.

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SUMMARY

Recurrence risks for the generalised single locus model and for the multifactorial model have been derived and compared. First the areas of overlap for the two models were determined and sets of parameters chosen to represent these overlap areas. Certain sets of parameters for the single locus model give recurrence risks in sibships similar to these for multifactorial inheritance. Other sets (representing very low penetrant dominant genes) give markedly lower risks. Similar results hold for more complex family histories. Empiric risks for families with two or more

affected individuals are needed so as to indicate the trend of the increase in risk which could then be extrapolated to other families and be used in genetic counselling.

RESUME

Les risques de récurrence pour une hérédité mendélienne et pour une hérédité multifactorielle ont été comparés. En premier lieu, les zones de chevauchement des deux modes héréditaires ont été déterminées et des séries de paramètres ont été choisies pour représenter ces zones. Certaines séries de paramètres pour une hérédité mendélienne donnent, dans des fratries, des risques de récurrence similaires à ceux calcules pour une hérédité multifactorielle. D'autres (représentant des gènes dominants à pénétrance très réduite) donnent des risques remarquablement plus bas. Des résultats semblables sont obtenus pour des pedigrees plus complexes. La connaissance des risques empiriques pour des familles ayant plus d'un individu atteint est nécessaire, afin d'obtenir une idée de l'accroissement du risque de récurrence avec le nombre d'individus atteints et pouvoir ainsi extrapoler le risque pour d'autres familles lors de conseils génétiques.

ZUSAMMENFASSUNG

Die Wahrscheinlichkeitsziffern für das Wiederauftreten von Geburtsanomalien sowohl beim Mendelschen als auch beim multifaktoriellen Modell, werden miteinander verglichen. Zuerst wurden die Ueberschneidungsbereiche der beiden Modelle bestimmt und Parameter-Sätze zu deren Darstellung ausgewählt. Bestimmte Parameter-Sätze für das Mendelsche Modell zeigen ein Wiederauftretungsrisiko für Geschwister ähnlich dem für multifaktorielle Vererbung. Andere Parameter, die besonders dominante Gene mit schwacher Penetranz betreffen, zeigen auffallend geringere Risiken. Aehnliche Ergebnisse gelten für mehr komplexe Stammbäume. Empirische Risiken für Familien mit zwei oder mehr betroffenen Mitgliedern sind notwendig, um den Trend des Risikoanstiegs anzuzeigen. Dieser kann dann für andere Familien extrapoliert und für die genetische Beratung verwendet werden.

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